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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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October 8, 2014
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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JEFFREY A. BRINKER, M.D.	Temporary Voting Member
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PATRICK T. NOONAN, JR., M.D.	Temporary Voting Member
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DEBRA McCALL, B.S., M.A.M.	Patient Representative
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M E E T I N G

(8:01 a.m.)

DR. PAGE: Good morning. It's now just after 8:00, and I'd like to call this meeting of the Circulatory System Devices Panel to order.

My name is Richard Page. I am a cardiac electrophysiologist, and I am Chair of the Department of Medicine at the University of Wisconsin in Madison.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application regarding the Boston Scientific WATCHMAN left atrial appendage, or LAA, closure technology.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

May I start with you, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. Good morning. Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

DR. SLOTWINER: David Slotwiner, electrophysiologist, North Shore-Long Island Jewish Hofstra School of Medicine.

DR. CIGARROA: Good morning. Joaquin Cigarroa, interventional cardiologist, clinical chief and clinical professor of the Knight Cardiovascular Institute at OHSU.

DR. KELLY: Patricia Kelly. I am a cardiac electrophysiologist in Missoula, Montana.

DR. NOONAN: Patrick Noonan, interventional neuroradiologist, Scott & White, Temple, Texas.

DR. YUH: Good morning. David Yuh, Chief of Cardiac Surgery at Yale University.

DR. LANGE: Good morning. My expertise is in interventional cardiology. My name is Rick Lange, and I'm president of the Texas Tech University Health Science Center in El Paso.

MS. WATERHOUSE: Jamie Waterhouse. I am a Designated Federal Officer for FDA.

DR. FURIE: My name is Karen Furie. I am a vascular neurologist and Chief of Neurology at the Alpert Medical School of Brown University.

DR. BRINDIS: Ralph Brindis, a recovering interventional cardiologist, UCSF, outcomes research and registries.

DR. NAFTEL: I'm David Naftel. I'm Professor of Surgery and Professor of Biostatistics at the University of Alabama at Birmingham, and I am a statistician.

DR. KANDZARI: Good morning. I'm David Kandzari. I'm the Chief Scientific Officer and Director of Interventional Cardiology at the Piedmont Heart Institute in Atlanta, Georgia.

DR. PATTON: Good morning. I'm Kristen Patton. I am a cardiac electrophysiologist at the University of Washington.

MS. McCALL: Good morning. I'm Debra McCall. I'm the Patient Representative and a volunteer at StopAfib.org.

MS. CHAUHAN: Good morning. Cynthia Chauhan, Consumer Representative.

MR. THURAMALLA: Good morning. I'm Naveen Thuramalla. I'm the Vice President

of Engineering and Clinical Studies at Transonic, a company located in Ithaca, New York. I'm serving as the Industry Representative.

DR. PAGE: Thank you very much. And I will point out that the Panel already is showing great expertise in microphone control. I will ask that everyone turn on the microphone just as they're called on to speak and turn it off as soon as you're done. That really improves the acoustics for all of us listening.

The other thing I'll mention today is we have a lot to do and very important work to do, and we have a limited time allotted. I'll be asking everyone to keep their own comments concise.

In terms of the agenda, I'll be asking the Sponsor and the FDA to stay to the time limits allowed that have been set well in advance.

And, finally, we have an unusually active open public comment section later in the day, and I just want to give a heads-up. There will be 4 minutes, no more than 4 minutes, for every speaker who addresses the Panel. That's the only way we'll be able to get that job done within an hour.

The final thing. I'll just remind the Panel of the importance of our work and the importance of hearing your voices as part of the discussion that other people can hear. So I'll ask for there to be no side conversations among the Panel. And, obviously, every time we go on break, we are called upon not to discuss the matter at hand.

So, with that, I'll remind everyone that if you have not already done so, please sign the attendance sheets that are on the tables by the doors.

And Jamie Waterhouse, the Designated Federal Officer for the Circulatory System

Devices Panel, will now make some introductory remarks.

MS. WATERHOUSE: Good morning. I will now read the Conflict of Interest and Deputization to Temporary Voting Member Statements.

The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section

208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application for the WATCHMAN LAA closure technology sponsored by Boston Scientific. FDA is seeking Committee review and recommendations regarding new clinical data and associated additional adverse events, including stroke, that have become available since the previous Advisory Committee meeting on the WATCHMAN device, which was held December 11th, 2013. The WATCHMAN LAA closure technology is a percutaneously delivered permanent cardiac implant placed in the left atrial appendage. This device is indicated to prevent thromboembolism from the left atrial appendage. It may be considered for use in patients with non-valvular atrial fibrillation who are eligible for warfarin therapy to reduce the risk of stroke and systemic embolism.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208.

Naveen Thuramalla is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Transonic Systems.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from

such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Circulatory System Devices Panel for the duration of this meeting on October 8th, 2014:

Dr. Ralph Brindis, Dr. Jeffrey Brinker, Dr. Joaquin Cigarroa, Dr. Karen Furie, Dr. David Kandzari, Dr. Patrician Kelly, Dr. Patrick Noonan, Dr. Kristen Patton, Dr. David Slotwiner.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This has been signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on September 24th, 2014.

For the duration of the Circulatory System Devices Panel meeting on October 8th, 2014, Ms. Debra McCall has been appointed as a Temporary Non-Voting Patient Representative. For the record, Ms. Debra McCall serves as a patient representative for the Cardiovascular and Renal Drugs Advisory Committee in the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this

meeting.

The appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on October 2nd, 2014.

Before I turn the meeting back over to Dr. Page, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is (410) 974-0947.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Morgan Liscinsky.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time. Thank you very much.

Dr. Page.

DR. PAGE: Thank you, Ms. Waterhouse.

We'll now proceed to the Sponsor's presentation. I would like to invite the Sponsor to approach the lectern.

I will remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will have 90 minutes to present. You may now begin your presentation.

Welcome.

DR. STEIN: Good morning, Mr. Chairman, members of the Committee, members of FDA. My name is Ken Stein, and I'm the Chief Medical Officer for Rhythm Management at Boston Scientific.

Today we will present updated results and analyses from the WATCHMAN clinical program. WATCHMAN is designed to offer another treatment option to reduce the risk of thromboembolism in carefully selected patients with high-risk non-valvular atrial fibrillation.

By way of background, in 2009, the device received a positive Panel recommendation based on early data from PROTECT AF. We worked interactively with the Agency to address the Panel's specific concerns, which included starting a second randomized trial: PREVAIL.

In May of 2013, the original PMA was filed, and in December of 2013, less than a year ago, a second Panel was convened. At this second Panel, we presented the 4-year PROTECT data, primary endpoint data from PREVAIL, and data from a continued access registry, and the Panel returned an overwhelmingly positive vote, 13 to 1, in favor of safety,

efficacy, and a positive benefit-risk profile for the device. Subsequently, we have provided updates to FDA detailing the additional WATCHMAN trial experience since the PMA submission. We're here today to review that additional data.

There have been a total of 15 new primary efficacy events in PREVAIL: stroke, systemic embolism, or cardiovascular death. Ten of these occurred in the WATCHMAN arm and five in the warfarin group. This is exactly balanced based on the 2:1 randomization in this trial. We will provide more detail on all of the new events. We will address any perceived divergence between randomized groups in PREVAIL, and we will discuss the consistency of performance of the WATCHMAN device across all of the trials.

The device itself has not changed since the first Panel review in 2009. WATCHMAN is permanently implanted at the opening of the left atrial appendage. It consists of a self-expanding nitinol frame with fixation anchors and a permeable fabric cover.

Overall, the procedure takes about an hour. WATCHMAN is implanted using a catheter-based delivery system via transseptal approach, similar to other interventional procedures in the left atrium, like AF ablation.

First, a transseptal cannula is inserted through the femoral vein. Under fluoroscopic and transesophageal echo guidance, the intra-atrial septum is crossed and the cannula guided to the left atrium. A guide wire is placed in the left upper pulmonary vein, and the access sheath and dilator are advanced over the wire into the left atrium. The guide wire is then removed from within the access sheath, and a pigtail catheter is carefully advanced into the left atrial appendage. The access sheath is advanced into the left atrial appendage using radiopaque marker bands to guide placement, and contrast and echo imaging are

used to confirm device sizing. Then the pigtail catheter is removed and is replaced with the WATCHMAN device. The access sheath is retracted to deploy the device, and before releasing the device, the implanting physician checks the position, anchor, the size, and the seal of the device by fluoroscopy and by transesophageal echo. Once satisfied with the proper position and fit, the physician unscrews the core wire and releases the device, and within weeks following the procedure, the body begins to form a layer of endothelial tissue across the face of the device.

Following successful implant, patients are prescribed warfarin and low-dose aspirin for 45 days. At that time patients undergo a transesophageal echo evaluation to assess for residual flow around the device. Adequate appendage seal is defined as residual flow less than or equal to 5 mm. If that seal is achieved, patients are then eligible to replace warfarin with clopidogrel. At 6 months, clopidogrel is discontinued and patients are instructed to continue aspirin indefinitely. If an adequate seal is not obtained at the 45-day TEE, periodic reassessments are recommended and patients continue on warfarin until an adequate seal is attained and then transitioned to aspirin.

Based on this post-implant treatment strategy, patients must be eligible for warfarin in order to be suitable candidates for WATCHMAN, as outlined in our labeling. Let me share with you this labeling which we developed in close collaboration with FDA:

"The WATCHMAN LAAC Device is indicated to reduce the risk of thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism."

We've added a sentence to our intended use, emphasizing that "In considering the use of WATCHMAN, the benefits and risks of the device and the rationale for an alternative to chronic warfarin therapy should be taken into account." We added this to explicitly highlight the need for physicians and patients to discuss individual benefits and risks and to carefully review the reasons for seeking an alternative to warfarin in deciding whether WATCHMAN implantation is appropriate.

These changes address the feedback from the 2013 Panel and make it clear that the device should not be viewed as a broad first-line replacement for oral anticoagulants. Patients and physicians should view WATCHMAN as an alternative for those who are eligible for warfarin but who have individual reasons to seek another long-term therapeutic option. Today we will review the totality of data from the WATCHMAN clinical program supporting this.

First, we will provide safety results from past panels and add new CAP2 data on the safety in over 500 patients. Then we will provide updated efficacy data for all of the trials and show that device performance has been consistent across the portfolio. Finally, we will show you a number of supplementary analyses. These additional analyses were all done either at the request of FDA in direct response to Agency questions or in response to questions asked at the last Panel.

Here is a more detailed agenda for our presentation today. Dr. Shephal Doshi from Pacific Heart Institute will discuss the urgent medical need for an alternative to long-term oral anticoagulation. He will also review the design of the WATCHMAN studies. Dr. Vivek Reddy from Mount Sinai Medical Center will then provide a recap of the trial results

presented to you at the Panel in December 2013 and will present the updated data and the new analyses since the last Panel. I will return to discuss our post-approval plans. And, finally, Dr. Kenneth Huber from Saint Luke's Mid America Heart Institute will wrap up the presentation with a discussion on the positive benefit-risk profile of WATCHMAN.

We have a number of additional experts with us to help address your questions. All external presenters and experts have been compensated for their time and travel.

And I am now pleased to introduce Dr. Shephal Doshi.

DR. DOSHI: Thank you, Dr. Stein.

Good morning. My name is Shephal Doshi, and I am a Director of Electrophysiology at the Pacific Heart Institute in Santa Monica, California. I have been a principal investigator on all of the U.S. WATCHMAN trials: PROTECT AF, CAP, PREVAIL, and CAP2. I have been implanting the WATCHMAN device since 2005. I'm here to talk to you about the unmet need for an alternative to long-term oral anticoagulation in non-valvular atrial fibrillation patients.

Stroke and A-fib are huge problems in terms of the number of patients affected and are also associated with increased morbidity and mortality. A-fib increases the risk of stroke four to five times greater than that of people in normal sinus rhythm. In fact, atrial fibrillation is responsible for 15% to 20% of all strokes, particularly in the elderly. But not only does A-fib dramatically increase the stroke risk, strokes in these patients tend to be larger and more likely to result in greater disability. These cardioembolic strokes are also more likely to result in severe hemorrhagic transformation. This is associated with an increased risk of death or recurrent stroke.

Let's look at how thromboembolic strokes develop in A-fib patients. In A-fib, relative stasis of blood creates an environment conducive to thrombus formation in the left atrial appendage. When this thrombus occurs, it is an independent predictor of TIA and ischemic stroke.

In 2000 a seminal series of TEE and autopsy data demonstrated that in non-valvular A-fib, 90% of the left atrial thrombus originated in the left atrial appendage. These thrombi can form and then dislodge, resulting in a cardioembolic stroke.

In this classic series of images, Panel A shows a thrombus which was formed within the left atrial appendage due to stagnant blood flow. Panels B through D document dislodgment and actual movement of that thrombus. This thrombus can then embolize to the brain or somewhere else in the body, resulting in a stroke or systemic embolism.

Now, to prevent these clots from forming in the first place, the standard of care is to first assess the patient's stroke risk and, if necessary, treat with a systemic anticoagulant. Up until this year, guidelines used the $CHADS_2$ score to assess clinical stroke risk. The latest revision of the ACC/AHA/HRS guidelines now incorporate a more refined tool to characterize stroke risk, the CHA_2DS_2-VASc score.

To provide some context, a CHA_2DS_2-VASc score of 1 is associated with an annual stroke risk of 1.3%, while a score of 2 or greater is associated with an annual stroke risk of 2% to 24%. The current guidelines recommend consideration of either warfarin or novel oral anticoagulants, or NOACs, for patients with a CHA_2DS_2-VASc score of 1 or greater. However, as I will show you, neither of these options is adequate to meet the need of all high-risk patients.

Ultimately, the guidelines recognize that when selecting treatment, clinicians have to balance the benefit of oral anticoagulation versus a bleeding risk. One of the most severe bleeding complications, particularly with warfarin, is intracerebral hemorrhage. This can be a spontaneous intraparenchymal hemorrhage, as seen in the first image, or can result from hemorrhagic transformation of an ischemic stroke, as seen in the second image.

Hemorrhagic strokes are generally much more disabling than ischemic strokes. And in anticoagulated patients, intracerebral hemorrhage is usually catastrophic. Importantly, fear of brain hemorrhage or death impacts the patient's adherence to therapy and also a physician's willingness to prescribe anticoagulants in the first place.

A review of 30 studies examined physicians' attitudes for prescribing warfarin for AF and identified bleeding risk and age as the most cited reasons for its underuse. Other factors associated with unwillingness to prescribe warfarin include a history of falls, a high risk of falls, comorbidities, and poor compliance. These fears leave many high-risk patients untreated. In fact, as stroke risk increases, the use of warfarin decreases. Data from a large Medicare database shows the percentage of patients using warfarin actually declined with increasing risk of stroke. Nearly 50% of the highest-risk patients remain untreated.

Although NOACs help, they don't solve the problem entirely. In pivotal trials of the three NOACs, discontinuation rates were between 21% to 24%. In fact, this is the same discontinuation rate as for warfarin in the same trials. Regardless of the anticoagulation drug used, more than one in five patients discontinued use within 2 years of starting.

Even with the new agents, major bleeding is still a risk. Major bleeding rates on the NOACs range from 2.1% to 3.6% per year, with only apixaban showing a lower annual rate

than warfarin control. In light of this bleeding risk and for other reasons, long-term anticoagulation therapy is underutilized for some patients.

Risk of stroke in A-fib patients represents a major public health problem, and as discussed, half of the high-risk patients remain unprotected from stroke. This is the unmet need. We need an alternative therapeutic strategy to reduce the risk of stroke in high-risk patients with A-fib, and for some of our patients, WATCHMAN can be that option.

I will now review the study design and patient characteristics in the WATCHMAN clinical program, specifically the randomized studies PROTECT and PREVAIL and the registries CAP and CAP2.

Enrollment in PROTECT began in 2005 and was completed in 2008. Patients were randomized 2:1 to either implantation of the WATCHMAN device or chronic warfarin therapy. The Sponsor then conducted CAP, a continued access registry. CAP used the same inclusion and exclusion criteria and the same procedure and treatment protocols as in PROTECT.

PREVAIL was initiated after the 2009 Panel meeting. Enrollment in this much smaller trial began in 2010 and was completed in 2012, with follow-up currently ongoing. Once PREVAIL enrollment was completed, the Sponsor then initiated a second continued access registry. The studies had similar follow-up schedules.

All trials used an identical composite efficacy endpoint in order to account for the different types of events that may be experienced in a high-risk population. The endpoint was designed to show clinical comparability of WATCHMAN to warfarin for the occurrence of stroke, systemic embolism, and cardiovascular or unexplained death. This primary

efficacy measure was developed in collaboration with FDA and represents a comprehensive assessment of the therapy, which reflects the intent of the WATCHMAN.

There were a few differences between the randomized studies. One difference to note is that PREVAIL modified the $CHADS_2$ inclusion criteria to enroll a higher-risk patient population. PREVAIL also excluded patients who had taken clopidogrel within 7 days before enrollment to avoid any potential confounding effects. Finally, the endpoint timelines were refined to separate the procedure-related events from long-term efficacy, and enrollment milestones were included for new operators.

All trials were developed in collaboration with FDA and followed the Agency's guidance on the use of Bayesian statistics. Bayesian methods allow for incorporation of prior established clinical data, thus requiring smaller sample sizes and limiting patient exposure to an experimental treatment.

As the pivotal approval trial, PROTECT AF was the largest in the clinical portfolio and was the basis of the informative prior for PREVAIL. Let me remind you that both studies utilized the same device, the same control therapy, and the same primary efficacy outcome. Without this informative prior, PREVAIL-only data are not powered to make robust conclusions. The pre-specified primary analysis of PREVAIL was presented in December, so any updated analyses presented today are post hoc.

Now, to review patient enrollment and demographics. A total of 2,406 patients have been enrolled in the WATCHMAN clinical program. Overall, we have 1,877 patients randomized or enrolled to receive a WATCHMAN device, and the majority of the implanted patients come from the PROTECT and CAP studies. As you can see, roughly 75% of the

randomized patient follow-up comes from PROTECT, with 2,717 patient-years of follow-up. In contrast, only a quarter come from PREVAIL, at 860 patient-years of follow-up. In addition, in terms of follow-up, the CAP registry has 2,022 patient-years and the CAP2 registry has 332 patient-years. In total, the clinical trials have almost 6,000 patient-years of data across four trials.

These trials enrolled a relatively older population with a mean age of 72 to 75. Two-thirds of the patients in these trials were male and they were primarily Caucasian. Looking at the risk factors for these patients, we see the $CHADS_2$ score increase with each subsequent trial. Remember, this was deliberate, based on the slight modifications to the inclusion criteria in the later trials.

In reviewing the individual components of the $CHADS_2$ score, I'd like to draw your attention to PROTECT as compared to PREVAIL and CAP2. There are increasing numbers of patients over the age of 75, those diagnosed with diabetes, and those who have experienced a previous stroke or TIA. And as we look at the continuous CHA_2DS_2-VASc scores, we see the same increasing trend with subsequent trials, with scores ranging from 3.5 in PROTECT up to 4.5 in CAP2.

If we look at this in a different way, we see that 93% of patients in PROTECT had a CHA_2DS_2-VASc score of 2 or more. This overwhelming majority of PROTECT patients are considered high risk according to the more contemporary and more sensitive indicator of stroke risk. Similarly, 96% of the CAP patients and all PREVAIL and CAP2 patients had scores of 2 or more, and all patients in all of the trials had a CHA_2DS_2-VASc score of at least 1, indicating that all of the patients were eligible for warfarin therapy under current

guidelines. But as I've mentioned, the guidelines recommend that stroke risk be balanced with bleeding risk before determining suitability for anticoagulation.

The HAS-BLED score is a tool used to assess bleeding risk. Patients with a HAS-BLED score of 3 or greater have a risk of major bleeding of more than 5% per year. In the WATCHMAN trials, five of the seven HAS-BLED components were prospectively collected. We calculated the HAS-BLED score by assigning zero points for the remaining values to yield a more conservative estimate of bleeding risk in our population. These HAS-BLED scores demonstrate that over 90% of the patients in all WATCHMAN trials had a moderate to high risk of bleeding.

To provide some context, in a study of 7,000 A-fib patients treated with anticoagulants in the SPORTIF III and IV trials, 24% of patients had a HAS-BLED score of 0. This difference in baseline HAS-BLED score between WATCHMAN trials and SPORTIF suggests that patients may have enrolled in the WATCHMAN trials seeking an alternative to long-term anticoagulation due to their risk of bleeding.

Now that we have reviewed the trial design and patient characteristics, I will turn the lectern over to Dr. Vivek Reddy to discuss the results from the trials.

DR. REDDY: Thank you, Dr. Doshi.

Good morning. My name is Vivek Reddy, and I am a professor of medicine and an electrophysiologist at Mount Sinai Medical Center in New York. I'm also a national principal investigator in PREVAIL. I am a consultant to Boston Scientific and other companies that manufacture left atrial appendage devices. I have no equity stake in any of these companies.

I'll now present comprehensive results from the WATCHMAN clinical program. First, I'll review the safety performance across the trials. Next, I'll review the efficacy data for PROTECT after 5 years of follow-up. In addition to PROTECT, you'll see an updated dataset for PREVAIL. The overall primary efficacy results look similar to what you saw in 2013. Finally, in an effort to synthesize the results of PROTECT and PREVAIL in a comprehensive manner, I'll show you a patient-level meta-analysis that summarizes the totality of the randomized data. Over the course of this section you'll see that the totality of the data strongly support the device as a comparable alternative to warfarin for the prevention of stroke, systemic embolism, and cardiovascular death. This composite endpoint was consistently applied to all WATCHMAN clinical trials and registries.

I'll also provide detail on the individual components of this combined efficacy endpoint. However, remember that these individual components were not independently primary endpoints, so it's very important to recognize that it's the composite endpoint that most fully assesses the efficacy of the WATCHMAN device. First, let's review the safety data.

At the December 2013 Panel, we demonstrated an improved procedure safety profile over the course of the clinical studies. In order to evaluate safety events across the studies, we used a consistent definition of all device- or procedure-related serious adverse events within the first 7 days.

Within PROTECT itself, the safety event rate decreased by over 50% from the first half to the second half of the study, reflecting increased operator experience and training. This lower safety event rate, between 4% to 5%, was maintained throughout the

subsequent trials: CAP and PREVAIL. Since that time we have new safety data from the 579 patients enrolled in the CAP2 registry, showing again a low complication rate, only 3.8%. These rates are similar to other interventional procedures, like catheter ablation for atrial fibrillation.

Unlike PROTECT, PREVAIL had a pre-specified 7-day safety endpoint. The pre-specified primary safety endpoint included death, ischemic stroke, systemic embolism, or any complications requiring surgical or major endovascular intervention within the first 7 days of the procedure. By the 2013 Panel, all implants in PREVAIL were complete, so this endpoint remains unchanged. The event rate was 2.23% with an upper credible interval of 2.65%. Since the performance goal was 2.67, PREVAIL did meet the safety endpoint.

Now, as Dr. Doshi mentioned, all updated efficacy analyses presented today are post hoc. These additional analyses were performed either at the request of FDA in direct response to Agency questions or in response to questions asked at the last Panel.

Let's first look at the efficacy in PROTECT data, the largest randomized trial, which has now completed follow-up at 5 years. Recall that the intent of all of these trials was to demonstrate that WATCHMAN was comparable to warfarin for the composite endpoint of stroke, systemic embolism, and cardiovascular death.

This table compares PROTECT AF results shown at the 2013 Panel with the 5-year results that we now have, which includes 2,717 patient-years of follow-up. You see that the rate ratios are consistent and continue to demonstrate not only non-inferiority but superiority for the composite primary efficacy endpoint. The posterior probability was at least 95% in both 2013 and the updated 2014 analyses. So these long-term results have not

substantially changed since the last time this Panel reviewed this data.

Let's now examine the individual components of this composite endpoint. In the WATCHMAN group there were 2.2 events per 100 patient-years as compared to 3.7 in the warfarin group, giving us a rate ratio of 0.61, representing a 39% reduction with the WATCHMAN device.

For all strokes, the annualized rates go from 1.5% in the WATCHMAN arm to 2.2% in the warfarin arm. This translates to a 32% relative reduction with a 99.9% posterior probability of non-inferiority.

Now, while not statistically significant, we also see a numerically higher rate of ischemic stroke in the WATCHMAN arm. In PROTECT, this was driven primarily by procedure-related strokes that occurred early in the trial. But WATCHMAN also demonstrated an 85% reduction in hemorrhagic stroke. So we see the rates of ischemic and hemorrhagic stroke going in different directions.

How can we grade the relative importance of these various types of stroke events? One option commonly employed in stroke prevention trials is to examine the functional impact on patients' lives, that is, the level of disability resulting from these strokes. To address this, we used the modified Rankin score, pre- and post-stroke, for those patients who experienced an event. This score is commonly used to quantify the disability resulting from a stroke. The scale ranges from a scale of zero -- from a score of 0, representing no disabling impact, to 6, representing death. In general, a change of 2 or more is considered disabling.

Using that definition, we present the stroke data dichotomized between disabling

and non-disabling strokes. We see that the annualized rates of non-disabling strokes are similar between the randomized arms: 1.1% for WATCHMAN and 0.9% for warfarin. However, the rate of disabling strokes in the warfarin group, 1.3%, is three times that of WATCHMAN at 0.4%, and this was statistically significant with a p-value of 0.02.

Returning to the components of the primary efficacy endpoint, we're left with systemic embolism and cardiovascular death. Now, systemic embolisms were rare, but for cardiovascular death, arguably the most important component of this primary endpoint, the annualized event rate was 1% for WATCHMAN compared to 2.3% for warfarin. The rate ratio was 0.44, favoring WATCHMAN, and this was statistically significant.

Now, at 5 years, 3.9% of patients died of cardiovascular causes in the WATCHMAN group compared to 9% in the warfarin group. So what drove this difference in mortality? It was primarily driven by a significant reduction in death related to hemorrhagic stroke. It occurred in 0.4% of patients in the WATCHMAN arm and 3.3% of patients in the warfarin arm. Now, this shouldn't be surprising. WATCHMAN allows patients to discontinue chronic warfarin. As a result, it provides comparable stroke reduction to warfarin without the risk of catastrophic hemorrhagic complications associated with chronic anticoagulation. Indeed, this is completely consistent with the NOAC trials. NOACs also confirm mortality benefit over warfarin, also driven by a reduction in hemorrhagic stroke.

Before we finish with the PROTECT long-term results, I would like to briefly return to the composite primary efficacy endpoint to address one specific point raised by the FDA, and this is specifically the high hemorrhagic stroke rate in the warfarin arm of PROTECT AF. The Agency notes that this rate is higher than that seen in the warfarin arms of the NOAC

trials. But, remember, the patients in NOAC trials were enrolled because they were good candidates for long-term anticoagulation. And as Dr. Doshi already mentioned, the HAS-BLED distribution in the WATCHMAN trials is quite different from that seen in the typical population getting anticoagulants. In PROTECT, only 6.4% of patients were low risk as compared to 24% in the SPORTIF studies.

So despite similar inclusion and exclusion criteria to the anticoagulation trials, patients in PROTECT were at a higher risk for bleeding, and this could explain the higher hemorrhagic stroke rate. In any event, it remains true that in the PROTECT warfarin arm, the hemorrhagic stroke rate of 1.1% is approximately double that seen in the NOAC trials, and the 0.2% rate in the WATCHMAN arm represents an 85% reduction in the hemorrhagic stroke rate. But even if the warfarin hemorrhagic stroke rate was hypothetically reduced to 0.5%, there would still have been a substantial reduction in hemorrhagic stroke with WATCHMAN.

Additionally, in order to conservatively assess the robustness of these PROTECT AF results, we performed a sensitivity analysis. We removed all of the hemorrhagic strokes and any subsequent events from only the warfarin arm. We even removed hemorrhagic strokes that occurred and that later resulted in cardiovascular death. Even in this conservative analysis, we see that WATCHMAN would still maintain non-inferiority for the primary efficacy endpoint. The relative risk reduction is 13% and the posterior probability for non-inferiority would still be over 99%.

Let's now turn to the efficacy performance in CAP, the next largest dataset, with 566 patients and 2,022 patient-years of follow-up. This is a Kaplan-Meier curve showing both

the CAP and the PROTECT composite primary efficacy endpoint. In red, you see the device performance in CAP; in green, the device arm of PROTECT AF. The CHA_2DS_2-VASc score in CAP was 3.9 and in PROTECT it was 3.5. Despite this higher score in CAP, the curves overlap. These curves demonstrate the relatively stable WATCHMAN event rates over long-term follow-up. For both of these large studies, the Kaplan-Meier estimates show no signal, they show no signal of increased risk of late events over the course of long-term follow-up for WATCHMAN patients.

We'll now examine the results from the second smaller randomized trial: PREVAIL. We'll discuss the new events that have occurred since the 2013 PMA submission dataset and will detail these events as part of the composite efficacy endpoint. I'll first review the definition of the primary analysis and the results presented at the 2013 Panel.

In addition to the safety endpoint that we've discussed, there were two efficacy endpoints in PREVAIL, designed to be evaluated when all patients had reached the 6-month time point. This is the analysis that was already presented at the December 2013 Panel. The first was a composite just like the other trials: stroke, systemic embolism, and cardiovascular death. The second was a measure of ischemic-only stroke and systemic embolism beyond the 7-day post-implant period. The endpoints were calculated using a modeled 18-month event rate based on a piecewise exponential analysis and included the discounted PROTECT AF data as an informative prior.

At the December Panel, the first efficacy endpoint was not met. The rate ratio was 1.07, but the credible interval was wide with an upper bound of 1.89. This did not meet the non-inferiority criterion, and the posterior probability was 93%.

For the second efficacy endpoint, the rate difference was 0.0053, again with a wide credible interval. But in this case the upper credible interval, 0.0273, was just under the pre-specified upper credible bound to declare non-inferiority.

Now, multiple evaluations of these efficacy endpoints were not pre-specified; however, we have recalculated them based on the new events since the last analysis. As in 2013, the first efficacy endpoint is still not met, with a rate ratio of 1.21 and again wide credible intervals. The posterior probability for non-inferiority is the same as it was in 2013: 93%. Although this does not reach the threshold for non-inferiority, it does remain a high probability that's consistent with non-inferiority.

For the second efficacy endpoint, which was barely met in 2013, the rate difference is now 0.0163. The wide credible intervals remain but now cross the boundary for non-inferiority, that is, this endpoint is not met with the posterior probability for non-inferiority of 89.2%.

Let's look at the new events in more detail. There have been 10 new primary efficacy events in the WATCHMAN arm and 5 in the warfarin arm of PREVAIL. Recall that these patients were randomized 2:1 WATCHMAN to warfarin. So when looking at these events, it's critical to look at the rates rather than looking at the raw numbers in each arm. As you can see, these events occurred in roughly the same percentage of patients, 3.7% of WATCHMAN and 3.6% of warfarin patients. Again, let me underscore this. There have been an equivalent number of efficacy events between groups since the last meeting.

Now, PREVAIL was a small trial that was not powered to evaluate the individual components of this primary efficacy endpoint; however, the Panel has been asked to

comment on these. So drilling down into these components, here are the new events since the 2013 dataset. Across both arms of PREVAIL there have been eight new ischemic strokes, three hemorrhagic strokes, no systemic embolism, and six cardiovascular deaths. All of the new ischemic strokes occurred in the device arm. However, in the warfarin arm, after accounting for the 2:1 randomization, there were roughly four times the rate of hemorrhagic strokes and four times the rate of cardiovascular death.

Now, let's look at how each of these new stroke events affected the patients. Here's a full listing of all new stroke events since the PMA dataset. The top two-thirds of this chart shows the new ischemic strokes in the WATCHMAN arm. The new hemorrhagic strokes are shown on the bottom third of the slide. But how did these strokes impact the patients? As you can see from the imaging summaries, many of these ischemic strokes were small, and in terms of the associated disability using the modified Rankin score, in all but three patients the ischemic strokes were mild. In contrast, at the bottom, the hemorrhagic strokes were generally catastrophic.

Just as we did with PROTECT, we have dichotomized these strokes in PREVAIL and to those resulting in a large disability or death versus those that were non-disabling. Note that the table includes all events in PREVAIL, not just the new events. What we see is that for the worst strokes, the disabling strokes, there was no significant difference between the two arms in PREVAIL. The annualized rates were identical at 0.7% with a p-value of 0.88. So the excess ischemic strokes in the WATCHMAN arm of PREVAIL were largely non-disabling.

So where did this take us? On the one hand we have highly significant results in

PROTECT, but on the other hand we missed the two efficacy endpoints in PREVAIL. One interpretation would be that there's a divergence of WATCHMAN performance between the two studies, but this is not the case. In the following slides I'll show you several different analyses, and taken together, the device performance is consistent and remains unchanged from the last two Panels that have returned positive votes.

First, this slide will show that the WATCHMAN ischemic stroke rates are in line with the expected rates based on risk scores. This graph plots the ischemic stroke risk as events per 100 patient-years, seen on the y-axis, versus the $CHADS_2$ score -- the CHA_2DS_2-VASc score, shown on the x-axis. The dotted black line on top shows the expected stroke rate for untreated patients.

These rates were obtained from the 2012 Swedish AF cohort study of 180,000 patients and the 2014 patient decision aid document from the UK National Institute for Health and Care Excellence. The solid black line on the bottom shows the reduced stroke rate for patients treated with warfarin as a function of the CHA_2DS_2-VASc score. This is the amount of ischemic reduction that these patients experienced on warfarin in a large real-world Swedish registry.

Now, in the green and blue triangles, the 2013 ischemic stroke rates in only the WATCHMAN arms of the two randomized trials are shown. Note that these rates are consistent with the solid line; that is, after accounting for the CHA_2DS_2-VASc score, we see the same reduction in ischemic stroke as one sees with warfarin. And in 2014, both trials remain in line with expected rates.

To evaluate the consistency of WATCHMAN performance, let's also include both CAP

and CAP2. In this slide, in addition to the point estimates, you also see the 95% confidence intervals for the ischemic stroke rate in PROTECT, CAP, PREVAIL, and CAP2. The point estimate for PROTECT is 1.3%, and for CAP, 1.2%. And the confidence intervals are relatively narrow for both of these studies. Next, you see that the point estimates increase in PREVAIL and CAP2 to 2.3% and 2.7% annually. But, importantly, the mean $CHADS_2$ scores for these two studies were also higher. Note that because of the shorter follow-up, PREVAIL and CAP2 have wider confidence intervals. Taken together, these data demonstrate that the point estimates in the WATCHMAN arm are in line with the expected ischemic stroke rate for warfarin; that is, there is no statistical divergence in the WATCHMAN performance between the four trials.

As I mentioned, the primary efficacy measure for all of these trials is the composite of stroke, systemic embolism, and cardiovascular death. Again, this represents the most comprehensive assessment of the therapy. The primary annualized efficacy rates across the trials ranged from 2.2% to 4.3% with overlapping confidence intervals. Once the CHA_2DS_2-VASc scores are taken into account, we see that the WATCHMAN device performance is consistent. But remember, as Dr. Doshi discussed, many AF patients who are at high risk for stroke are left untreated because they are unwilling or unable to maintain adequate anticoagulation over the long term.

Therefore, the FDA asked us to perform an imputed placebo analysis to quantify how much benefit these otherwise untreated patients might see in terms of ischemic stroke reduction if they were treated with the WATCHMAN device. To do this, we estimated the relative reduction of ischemic stroke risk for WATCHMAN patients based on their average

$CHADS_2$ score.

For PROTECT, PREVAIL, and CAP, we know the $CHADS_2$ scores and we know the observed ischemic stroke rates. Then we used the $CHADS_2$-based predicted stroke rates in an untreated population. For these patient populations, this imputed annual stroke rate ranges between 5.6% to 6.7%. One can then estimate the relative reduction in ischemic stroke. So what we see is that WATCHMAN provides impressive reductions for these otherwise untreated patients, ranging from 65% to 81%. For reference, this is comparable to the reduction seen with oral anticoagulants like warfarin or the NOACs.

Of course, one of the limitations of this kind of analysis is use of historical controls. So, in order to test the robustness of this finding, we repeated this analysis using a more contemporary control population. We used the CHA_2DS_2-VASc scores in a reference population from a large Danish registry, published in 2011, of over 132,000 patients. For the study population, the imputed stroke rate was between 6.2% and 7.1%. And once again we estimated the relative reduction in ischemic stroke. What we see is that WATCHMAN again provides impressive reduction for these otherwise untreated patients, ranging from 67% to 83%.

These two imputed placebo analyses reassure us that we can expect a long-term benefit when WATCHMAN is used in the likely patient population, that is, those patients eligible for warfarin but have reasons to pursue an alternative treatment strategy.

So I've shown several slides demonstrating that WATCHMAN performance is consistent over the various trials and provides imputed benefit over no therapy. But if the WATCHMAN arms performed as expected, why did PREVAIL miss its two efficacy endpoints?

To answer this, we need to look at the unusual ischemic stroke rate of the warfarin arm.

Here we see that the warfarin ischemic stroke rates in PREVAIL differ from all other contemporary trials using warfarin as a control. With only one stroke in the warfarin arm of PREVAIL, the observed rate has a point estimate of only 0.3% with extremely wide confidence intervals. This rate is dramatically lower than the warfarin arms of the other major trials: PROTECT AF, RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE. And this occurred despite a higher $CHADS_2$ score or a high $CHADS_2$ score in PREVAIL. As is evident from the wide confidence intervals, the most likely explanation is a small sample size in PREVAIL; that is, merely chance. But certainly this slide highlights how implausible it would be to reproduce the PREVAIL warfarin group behavior in broad clinical practice.

Up to this point I've been talking about PROTECT and PREVAIL as two separate and, perhaps implicitly, somewhat equivalent studies. But the fact remains, they are not. The total number of patients and the duration of follow-up in PROTECT far exceeds that in PREVAIL. In fact, PROTECT represents over 75% of the randomized control data. PREVAIL represents less than a quarter. Of course, PREVAIL does contribute to the totality of data, but it must be viewed in the proper context and with the appropriate emphasis.

Now, FDA is asking us to evaluate the full totality of data. As Dr. Doshi mentioned, both randomized trials evaluated the same device with the same control and against the same primary endpoint, so we were able to perform a patient-level meta-analysis of all randomized control data. In the remaining slides I'll show you the results of this analysis of combined PROTECT and PREVAIL cohorts.

First, and most importantly, the composite primary efficacy endpoint. For the meta-

analysis, you can see that the hazard ratio is 0.79. This demonstrates comparable outcomes between the WATCHMAN and warfarin arms.

Let's now review the various components on the slides, starting with strokes. For all stroke or systemic embolism, there is no difference between the two treatments, with a hazard ratio of 1.02. As we examine the types of strokes, we see an advantage in ischemic strokes for the warfarin patients, but this is balanced by an advantage in hemorrhagic strokes for the WATCHMAN patients.

So how do we interpret these different types of strokes? Recall several slides ago I discussed that what really matters to patients is the impact on their lives, that is, the disability that results from the stroke. This slide shows us the combined disability analysis including all strokes in all randomized patients. We used the same criteria of an mRS change of 2 or more being disabling. While the overall number of strokes is similar between groups, there are significantly more disabling strokes in the warfarin arm versus the WATCHMAN arm. The annualized rates were 0.5% for WATCHMAN and 1.1% for warfarin. The hazard ratio of 0.44 represents a 56% relative reduction in disabling strokes with WATCHMAN. Again, there was no difference in non-disabling strokes between groups.

The final and arguably the most important component of the composite endpoint is death attributable to cardiovascular causes. The patient-level meta-analysis shows an advantage for WATCHMAN over warfarin. The hazard ratio was 0.48 and was clearly significant with a p-value of 0.006. In addition, for all-cause mortality the hazard ratio was 0.73, also in favor of WATCHMAN, with a p-value of 0.07.

Together, these mortality data, they highlight the advantages of avoiding long-term

warfarin and the attendant hemorrhagic risks associated with the drug. In fact, avoidance of long-term warfarin is a major goal of WATCHMAN implantation, and for most patients, this goal was achieved. Here we see that a small percentage of WATCHMAN patients, around 7%, had to transiently resume warfarin, usually due to medical procedures such as cardioversion or catheter ablation. But ultimately about 90% of device patients were able to avoid chronic warfarin. So the vast majority of WATCHMAN patients are not taking long-term warfarin.

What are the downstream benefits of this with respect to bleeding? To examine bleeding during the various phases of WATCHMAN implantation, we performed a landmark bleeding analysis of the combined cohorts and separated the bleeding events into four time intervals: the immediate periprocedural period during which pericardial bleeding occurred in the WATCHMAN group; the periods of up to 45 days and then 6 months when WATCHMAN patients were still mandated to take antithrombotic agents and the bleeding rates were similar; and the final period when WATCHMAN patients were on aspirin alone and the control patients were on chronic warfarin. This analysis shows that beyond the 6-month time point, there's a highly significant 71% reduction in the risk of major bleeding for WATCHMAN patients. This is of particular importance because it would be reasonable to expect the continued separation of these curves over the lifetime of the patient.

Beyond this time-dependent nature of these bleeds, let's look at the overall bleeding events. If you look at major bleeding within the temporal confines of these randomized trials, there's no significant difference between groups. However, if we again look carefully at the different types of bleeding, there's an excess of non-procedure related bleeds in the

warfarin arm; the hazard ratio of 0.51 and a highly significant p-value of 0.002.

From a clinical perspective, this is relevant because procedure bleeds, mainly pericardial effusions, can be dealt with immediately in the hospital setting. These events are less concerning than those that occur in an ambulatory setting where access to medical attention may not be immediate. So WATCHMAN demonstrates a significant reduction in major bleeding events not related to the procedure, that is, those that occur outside of a medical setting.

I'd now like to summarize and conclude the results portion of this presentation.

Just as in 2013, procedural safety endpoints have been met and confirmed in subsequent studies. Just as in 2013, PROTECT is superior for the primary efficacy endpoint. And just as in 2013, PREVAIL missed this primary efficacy endpoint. However, the device performance is consistent with the larger trials that did demonstrate non-inferiority.

And, finally, the patient-level meta-analysis allows the proper weighting between the two trials to evaluate the full totality of evidence and should leave no reasonable doubt as to the following four points:

First, WATCHMAN is comparable to warfarin for the primary efficacy endpoint of stroke, systemic embolism, and cardiovascular death.

Second, while ischemic stroke favors warfarin, WATCHMAN is clearly superior for hemorrhagic stroke, and as a result, WATCHMAN is superior for disabling stroke.

And, finally, WATCHMAN is superior for cardiovascular death.

This totality of data demonstrates that WATCHMAN is a safe and effective alternative for warfarin-eligible patients with non-valvular atrial fibrillation.

Dr. Stein will now return to discuss the Sponsor's post-approval training and study plans.

DR. STEIN: Thank you, Dr. Reddy.

At Boston Scientific we are committed to the safe and effective use of all of our products. This is not an idle statement. We have a long history of successfully training physicians on novel technologies, including the first endocardial ICD leads, cardiac resynchronization therapy, rotational atherectomy, and most recently the subcutaneous ICD.

Once WATCHMAN is approved in the U.S., we will implement the same level of rigor in training U.S. physicians. We are also committed to the rational dispersion of the technology through a disciplined and highly selective approach to center identification. Our rollout will be governed by the rate at which we can ensure a robust training experience. We will ensure that all implanters and implanting centers meet specific prerequisites: adequate facilities and a dedicated and experienced team to perform the procedure.

In addition, we will require implanters and echocardiographers to complete a rigorous clinical training program. Let me walk you through the mandatory four-phase training program. It will start with an online review of instructions for use, imaging techniques, clinical trial data with attention to patient selection, and implant videos.

Phase II will be a mandatory, in-person, one-day professional training event conducted by experienced physician faculty plus clinical specialists and training staff of Boston Scientific. We will review the didactic content from Phase I. Attendees will be trained on techniques for safe and effective implants, including the use of a virtual reality

transesophageal echo simulator, a virtual reality procedure simulator, and the use of 3-D printed heart models based on actual WATCHMAN patients. Beyond the technical aspects of the procedure, we will also pay attention to patient selection and to communicating benefit-risk considerations to patients, using tools available to enhance patient-centric decision making.

In Phase III, new operators will implant patients for the first time, supported by experienced Boston Scientific clinical specialists. In addition, we will provide all implanters the option of having an experienced physician proctor present for their initial cases.

In the final phase, operators transition to independence. Here, operators will continue to implant patients with ongoing support from clinical specialists for as long as necessary, just as we do throughout the world.

To complement this training program, we will conduct a robust post-approval trial. We continue to work with FDA to design this study to collect additional safety and real-world outcome data. Based on feedback from the 2013 Panel, we have increased the size of the post-approval study. Following approval, we will enroll 1,000 new patients who will be followed for 5 years with predefined performance goals. Also in response to suggestions from the 2013 Panel, we are incorporating a prospective analysis of bleeding complications, and we have established strategies to recruit a more diverse set of patients.

In summary, through a comprehensive training program based on proven methods that Boston Scientific has successfully employed around the world, a careful site selection process with a deliberate rollout cadence, and a rigorous post-approval study, Boston Scientific is committed to the safe and effective use of WATCHMAN in the U.S.

I'll now turn the lectern over to Dr. Huber, who will conclude our presentation.

DR. HUBER: Thank you, Dr. Stein.

And good morning. My name is Kenneth Huber, and I am a practicing interventional cardiologist at the Saint Luke's Mid America Heart Institute. Over the last 25 years I have cared for thousands of patients with atrial fibrillation and have participated in all the WATCHMAN trials and registries. In addition, my institution was one of the primary training sites for new implanters, and I personally trained one-third of the new implanting physicians for the PREVAIL trial.

I'm here today to share my clinical perspective on the challenges of benefit-risk assessment for the use of oral anticoagulation to prevent stroke in patients with atrial fibrillation, the limitations of the treatment options currently available, and why I believe the evidence presented today demonstrates that left atrial appendage closure with WATCHMAN has been proven to be an excellent, clinically acceptable alternative for some of these patients.

I want to be clear. Warfarin and now even more so the NOACs are highly effective first-line therapies for ischemic stroke protection in patients with atrial fibrillation. Those patients already doing well on these drugs, and who we anticipate will continue to do well on these drugs, should not be considered for WATCHMAN.

This benefit-risk decision is primarily based on the challenging task of balancing the patient's risk of stroke with their risk of bleeding. Currently validated risk models, as seen on this slide, CHA_2DS_2-VASc and HAS-BLED, serve as one way to begin to frame the discussion.

Let's take a patient with a CHA_2DS_2-VASc score of 3, where the annual stroke risk is 3.2%. Now, if that patient has a HAS-BLED score of 2, the annual bleeding risk is moderate at 4.1%. Although still quantitatively a greater percent annual risk of bleeding compared to that of stroke, it's likely that the physician would counsel the patient and family that the benefit-risk favors anticoagulation.

That said, there are other important patient variables to consider that are not reflected in the HAS-BLED score. These might include a patient's ability to adhere to a medication or a condition or a lifestyle that might put them at risk for trauma. These circumstances, unique to an individual patient despite the low HAS-BLED score, might sway that patient and family away from anticoagulation.

Another patient may have a HAS-BLED score of 4, where the annual bleeding risk is now nearly 9%. This high risk of bleeding relative to stroke, in the eyes of many patients and families and indeed physicians, would likely be considered prohibitive to long-term anticoagulation.

Now, remember, the HAS-BLED score we see here estimates annual risk of bleeding, but physicians and patients must then extrapolate this to a lifelong risk of bleeding on anticoagulation for 10 to maybe 20 years. So what might the 10-year risk look like? This slide shows a model of what we might reasonably expect in terms of 10-year bleeding risk as stratified by HAS-BLED score.

With that HAS-BLED 4 patient just mentioned, we're looking at around a 60% chance of major bleeding over the next decade. It is primarily this risk of long-term bleeding and often the difficulty in finding equipoise in these complex patients that results in nearly half

of our patients at the highest risk of stroke, those with $CHADS_2$ scores of 4, 5, and 6, as highlighted here, those that would potentially benefit the most from a proven therapy -- the most likely not to be treated, to be left unprotected. These patients and their families look to us for guidance and recommendations about options other than anticoagulants, and this is a very difficult conversation, frankly because no other satisfactory options exist.

Currently in the U.S., the only non-oral anticoagulation alternatives for these unprotected patients are antiplatelet therapies or procedures such as left atrial appendage ligation with LARIAT and/or cardiothoracic surgery. These therapies have either been proven inferior to anticoagulation or they lack large-scale randomized clinical trial data to support efficacy and safety. How to best counsel these patients and their families in light of the challenges of oral anticoagulation and the absence of any other effective option is the fundamental dilemma that indeed led to the idea of a local mechanical solution in the first place, the WATCHMAN device as a potential alternative to reduce stroke in these patients.

WATCHMAN does have randomized clinical trial data, so let's revisit this now. I believe that the most complete look at the totality of the data comes from the patient-level meta-analyses of both randomized trials that Dr. Reddy showed earlier. From a purely ischemic stroke protection perspective, warfarin outperforms WATCHMAN. However, for the reduced reduction of hemorrhagic stroke, WATCHMAN outperforms warfarin. But this combination results in a similar number of all strokes, with a hazard ratio of 1. Arguably the most important measure, cardiovascular death, is significantly reduced with WATCHMAN.

And as I've just discussed, it's the long-term risk of bleeding that is the primary driver of why patients may consider LAA closure, and here you see that, as expected, late

non-procedure related major bleeding is significantly reduced by WATCHMAN. So, collectively, from an overall clinical perspective, the combined primary efficacy data and major bleeding analyses support the conclusion that WATCHMAN is comparable to warfarin.

So, up until now, I focused on different ways of statistically interpreting the clinical relevance of the data using hazard ratios and p-values. However, under the recommendation of the Institute of Medicine and professional societies such as the ACC and AHA, we also recognize the importance of transitioning many of our benefit-risk discussions towards a more graphic patient-centered, evidence- and outcomes-based approach to shared clinical decision making. In response, I would like to now share with the Panel this potential model, a tool that might serve this purpose.

This is a 5-year model based on the PROTECT and PREVAIL meta-analysis data just reviewed. Examples very similar to this are already being used for other catheter-based therapies such as TAVR.

Each circle represents a single potential patient out of 1,000 treated with WATCHMAN, on the left, and warfarin, on the right. The three colors of the dots represent outcomes that contributed to the primary endpoints of the trials. Black represents cardiovascular death, including patients who had a fatal hemorrhagic stroke or fatal ischemic stroke. Red represents nonfatal hemorrhagic strokes and pink shows nonfatal ischemic strokes or systemic embolism, and no color represents event-free patients. The first thing we notice is that the vast majority of patients in both groups have no events. The second thing we notice is that warfarin patients have collectively more adverse events than

WATCHMAN patients.

So let's zoom in on these data to better reflect on each different component. Most strikingly, we see differences in cardiovascular death between the groups, again arguably the most relevant endpoint in evaluating comparative efficacy of any therapy. Patients on warfarin are more likely to die from a cardiovascular event than those in the WATCHMAN group. This finding has been consistent through both PROTECT and PREVAIL trials. In addition, WATCHMAN patients experienced fewer nonfatal hemorrhagic strokes, seen here in red. As we've discussed, hemorrhagic strokes are typically much more disabling than ischemic strokes, emphasizing the importance of this spread even further.

Now, as seen here in pink, WATCHMAN patients do experience more ischemic strokes and systemic embolisms than patients with warfarin. But despite this catch-up, the total number of bad events of death and strokes is still larger with warfarin than with WATCHMAN.

A similar 5-year shared clinical decision-making tool for bleeding is shown here. In yellow we see upfront major bleeding related to the procedure; in red, long-term major bleeding unrelated to the procedure. Despite this upfront procedural risk, warfarin patients will ultimately have a higher overall number of major bleeding events, and these rates of major bleeding would be expected to continue to diverge, in favor of WATCHMAN, over a patient's lifetime.

And before I conclude this presentation, I would like to specifically address why I believe the WATCHMAN does indeed reduce ischemic stroke as designed. This is a graphic representation of an imputed placebo analysis that Dr. Reddy showed earlier, which shows

how WATCHMAN and warfarin would be expected to perform relative to no therapy at all. Note that both WATCHMAN and warfarin substantially reduce the relative risk of ischemic stroke versus placebo to a similar degree: 75% with WATCHMAN and 83% with warfarin. This 75% reduction in ischemic stroke with WATCHMAN strongly supports the central role of thromboembolism from the left atrial appendage in the pathogenesis of ischemic stroke in these patients. The only plausible mechanism for the warfarin-like efficacy in the WATCHMAN arm is the ability to eliminate the left atrial appendage from the systemic circulation. This analysis reassures me that although non-left atrial appendage sources of ischemic stroke do exist in these patients, the collective data validate that WATCHMAN provides substantial protection against ischemic stroke in these patients.

So, to summarize and conclude our presentation, currently available alternatives to oral anticoagulation for U.S. patients with atrial fibrillation have either been proven inferior or lack randomized clinical trial data to support efficacy and/or safety. We need a proven alternative therapy for stroke management in patients who have a rationale not to take long-term warfarin. WATCHMAN meets that need.

The data presented today serve as the foundation for a patient-centered, shared clinical decision-making process that's necessary when treating these complex patients. The option to consider WATCHMAN is evidence based; it focuses on outcomes and acknowledges the challenges and tradeoffs inherent to this benefit-risk analysis. The data unequivocally support LAA closure with WATCHMAN as a clinically acceptable alternative to warfarin therapy for appropriately selected patients.

I thank you for your time and attention today, and I will turn the lectern back to

Dr. Stein to take your questions.

DR. PAGE: Thank you very much. I want to compliment the Sponsor for a very well prepared and clear presentation.

At this point we're able to ask the Panel for any brief clarifying questions for the Sponsor. Please remember that the Panel may also ask the Sponsor questions during the Panel deliberations in the afternoon. This is our one opportunity to specifically ask questions that might result in a little bit of homework over the lunch break. I want to limit that to very important issues.

I'm also going to make note, Dr. Zuckerman, that we will have a representative from FDA helping us keep track of whatever questions we have for the Sponsor so that at the end of the session before lunch, we're able to read those back and make sure that the Sponsor and the FDA are clear about the questions being asked. Are we prepared to do that, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. Dr. Nicole Ibrahim will work with the Sponsor to make sure we have all the questions collated.

The second point is, for the record, Dr. Jeffrey Brinker, Professor of Cardiology at Johns Hopkins, has joined our distinguished Panel this morning.

DR. PAGE: Thank you. And welcome, Dr. Brinker.

I'll now ask for the Panel to present any questions to the Sponsor.

Dr. Cigarroa.

DR. CIGARROA: Thank you. Again, thank you for the clear presentation this morning.

Two questions. It is known that hemorrhagic strokes are a major complication of antithrombotic therapy. Furthermore, it's known that when one combines antiplatelet therapy such as aspirin, that that rate is increased threefold and as well that hypertension and specifically mean blood pressures are associated with an excess risk of intracranial hemorrhage on warfarin therapy.

Do you have any data, in the patients assigned to the warfarin arm, as to whether (a) they were antiplatelet therapy and (b) whether there was any difference in blood pressures between the warfarin arm and the WATCHMAN arm?

DR. STEIN: Thank you. Let me answer the second part first. We did not record mean blood pressures and analyze them throughout the trial. So we do have data on the prevalence of hypertension, and as you can imagine, hypertension was quite prevalent and equivalent in both arms of the trials.

In response to the first question with respect to how many patients in the trial were on an antiplatelet therapy, specifically aspirin as well as on warfarin for those of them in the warfarin arm, we do have data on that. As I think you've seen in reading the Panel decks, there were a lot of cardiac comorbidities in these patients, so a large number of patients with history of coronary artery disease and a large number of patients with prior coronary intervention; in addition, a large number of patients who had prior stroke or TIA.

So just a second. I'm just going to pull up our demographics, and we'll show you just how many patients in the various trials were on aspirin at the time that they were enrolled into the trial. If you'll give me just one moment, we'll pull that slide up.

DR. PAGE: Dr. Stein, I think Dr. Cigarroa had a clarifying comment.

DR. STEIN: Sure.

DR. CIGARROA: So specifically in those who experienced the hemorrhagic event, did the -- do you have the data in the warfarin-assigned groups who experienced a hemorrhagic event --

DR. STEIN: I see.

DR. CIGARROA: -- how many of those were on antiplatelet therapy?

DR. STEIN: Yes, I've got the baseline data. In PREVAIL roughly 40% of the patients were on aspirin, and you can see the reasons why they were on aspirin. In PROTECT it's also that same, roughly 40% of the entire population. I don't have the breakdown right now, specific to those who experienced hemorrhagic stroke, and we can see if that's something we can get for you after the break.

DR. PAGE: Dr. Furie.

DR. FURIE: Thank you.

I have a question about the modified Rankin Scale. Can you describe the process of how those measures were obtained? Were they in person or by telephone? Were the personnel trained? And then I have a couple of scenarios I'd like you to comment on. If someone's score went from 0 to 2 or from 4 to 6, did you consider them disabled for this analysis?

DR. STEIN: Yes, let me again -- so the process. The mRS was adjudicated in person by a neurologist who was part of the study team. There were regular follow-up visits, as you can see here, and for the purpose of the mRS analysis, we're using the mRS score at the first regular follow-up after the event, trying to take into account what the chronic outcome

is from the event.

In terms of the question, so a change of 2 or more -- there were several that went from 0 to 2 or from 2 to 4 -- was included in this particular analysis, as was anything that resulted in death, even if it was a change of 5 to 6. But I think that answers the question.

DR. FURIE: So, just to clarify, the modified Rankin scores that you are reporting were immediately after the stroke or hemorrhage, not at 90 days, which is a more standard --

DR. STEIN: No, let me clarify. They were not immediately after. They were at the first routine follow-up after the event. So, actually, I can show you the median time from the event to the mRS determination. So, in PROTECT, that median time was 66 days. In PREVAIL, the median time was 87 days.

DR. PAGE: Okay, I've seen Dr. Yuh and then Dr. Noonan.

Dr. Yuh.

DR. YUH: Yes, thank you.

I just had a clarifying question referring to Slide 58, where you detail the ischemic and hemorrhagic strokes. Can you tell me, amongst those strokes, were they all at the aspirin-only phase of the trial or were there any differentiations with patients that were on Plavix and aspirin versus aspirin alone amongst those that incurred strokes?

DR. STEIN: So what we're showing here are the additional events since the last Panel. So these all came after everyone had finished 6 months, so these are all on the aspirin-only arm for those patients who were in the WATCHMAN group.

DR. PAGE: Thank you.

Dr. Noonan.

DR. NOONAN: Yes. Take a look at Slide Number 71, please. We have 6.2% of patients who, despite getting the device, had to go back on warfarin. So that's sort of a treatment failure. Now, can you break those down? For example, what percentage of those patients were in the PROTECT and what percentage in PREVAIL? Was it a matter of under-sizing the device? Perhaps operator inexperience? And do you have any data from CAP and CAP2 regarding the treatment failures?

DR. STEIN: I may just need you to clarify that, what you mean in that last question by treatment failures.

DR. NOONAN: Well, if you put the device in so you can get off warfarin --

DR. STEIN: Right.

DR. NOONAN: -- and you have to go back on warfarin, it's failed.

DR. STEIN: Yeah. No, I just wanted to make sure I understood that. So we can show you across some of the trials, you know, the reasons for long-term resumption of warfarin. I'm going to invite Dr. Reddy up to walk through that data, I think, for PREVAIL and PROTECT and then we'll see if we can pull that up for CAP. And I don't know that we have that in CAP2 at this point because the follow-up in CAP2 is so limited.

DR. REDDY: Thank you. Vivek Reddy, Mount Sinai Hospital.

In just a second we'll pull up the slide. Let's see here. Hold on. I'm going to pull up the slide that shows the percent success in the various clinical trials, if you'll just give us a second.

In general, the success has been pretty good. So, if you recall, in PROTECT, the success of implantation was around 90%, 92%. I'm fudging the numbers a little bit. I may

be off by a percent or so. But if you look in the subsequent trials -- and this is true in CAP, PREVAIL, and in CAP2 -- the success of implantation increased significantly. It's always been now around 95%, between 94 and 96.

Actually, here's a slide that shows the cessation rates in these three trials. So there's PROTECT, there's CAP, and there's PREVAIL. And, again, you'll see that the PROTECT numbers are a little bit lower. I don't think they reach statistical significance, but they're a little bit lower, and that's not terribly surprising as operators and the whole clinical program were learning exactly how best to implant. But over the course of the trials, you can see that the success in terms of ceasing warfarin has increased, and now it's clearly over 95%.

DR. PAGE: Dr. Lange.

And, Dr. Noonan, can you turn off your microphones, please? Thank you.

Dr. Lange and then Dr. Patton.

DR. LANGE: Again, thanks to the Sponsor for an excellent presentation.

On Slide 57 is displayed the data since the 2013 Panel, and I'm wondering if, at the time of the break, we could just see all of the data, that is, from the beginning of the study until the 2014 --

DR. STEIN: This is just the total number of individual events in the same framework.

DR. LANGE: Yes.

DR. STEIN: If you'll give me a moment, we may be able to pull that up right now. I believe that we have -- and indeed we do. So these are just the raw events, again, looking -- and, in fact, comparing what we presented in the 2013 Panel, in the left. I think to the far right is that one you just saw with the new events, and the center column or the center two

columns reflect that full totality, if you will, of the PREVAIL-only data. Again, I think it is important to emphasize and to remind everyone that there's a 2:1 randomization. And so if it helps, I can also show you those data in terms of rates rather than as raw numbers.

DR. LANGE: That would be very helpful.

DR. STEIN: Yeah. And so here are the data again for the PREVAIL-only population, expressed again as rates just as a way of making sure that we adjust for that 2:1 randomization.

DR. PAGE: Just so I'm clear, Dr. Lange, were you looking for a more granular description of the stroke events prior to the new data, or are you satisfied?

DR. LANGE: I'm satisfied. I mean, the two slides, the one that went by real fast and the one that went by slightly faster --

(Laughter.)

DR. STEIN: Maybe we can pull that one back up for just a moment.

DR. PAGE: Are you wanting those to be re-projected, Dr. Lange?

DR. LANGE: Yes, just for a second.

DR. STEIN: Yes.

DR. LANGE: Yes. And the previous slide as well.

DR. STEIN: Yeah, just tell me -- if you tell me when you're done with this, we'll pull up the other one.

DR. LANGE: Very helpful. Thank you.

DR. PAGE: And while you're looking at that, Dr. Lange, do you mind just telling us what you're seeing from that that's satisfying your question?

DR. LANGE: So this slide, particularly the middle panel, describes the total events from beginning until the 2014, where the events -- ischemic events, 13 in the WATCHMAN and 1 in the warfarin; hemorrhagic, 2 in the WATCHMAN and 2 in warfarin; and cardiovascular deaths, 8 versus 6. Then when you go to the percentages -- because again, this is a 2:1 randomization. So Slide 31 again, please -- it looks that the ischemic stroke rate is -- the overall stroke rate is 2.6-fold higher in WATCHMAN versus warfarin; ischemic stroke rate is 6.8% higher, or 6.8-fold higher; hemorrhagic rate, 0.5; and cardiovascular death, 0.7. And the p-values are displayed to the right. So that's very helpful. Thank you, sir.

DR. PAGE: Thank you.

Dr. Patton.

DR. PATTON: I'm still trying to reconcile the differences between the excess hemorrhagic stroke rate seen in the PROTECT trial and the very low ischemic stroke rate seen in the control group in PREVAIL, and I'm wondering if you can remind me of the time in therapeutic range for the two trials.

DR. STEIN: Yes, we can go over the time in therapeutic range. Actually, the time in therapeutic range in both PROTECT and PREVAIL was roughly comparable. It was 68% in PREVAIL and 70% in PROTECT AF. We're actually quite proud of what we were able to achieve in these trials. It's as good or better than in any other contemporary trial of stroke prevention in atrial fibrillation and certainly much better than is typically achieved in routine clinical practice. And I think it's just a testament to the dedication of the study coordinators, principal investigators, and treating physicians.

DR. PAGE: Dr. Brinker.

DR. BRINKER: Thank you.

Although the numbers of strokes are small, I wonder if all of them routinely had a TEE to evaluate whether there was flow through the atrial appendage.

DR. STEIN: They did not all have routine TEEs. Many of the patients with stroke presented to outlying hospitals rather than the investigating center. And so while they had imaging when they had the stroke, MRI -- or usually if MRI was not -- couldn't be done because of the presence of cardiovascular implanted devices, the CT scan. But of the ischemic stroke patients in PREVAIL -- and there were 14 of them -- 7 of them had TEE.

DR. BRINKER: Well, I have two pieces of that to follow up. Of those seven, was there any evidence that there might still be a patent atrial appendage, or was there a reason to think that the device might not be functioning optimally?

DR. STEIN: Yeah. So one of those seven patients had a device thrombus, and that was known and we had provided that data to FDA. Actually, that was before the last Panel. In terms of the other imaging, there was really nothing at all in any of the other patients on the imaging that would explain it in terms of a leak around the device or improper position of the device, et cetera.

DR. BRINKER: Good. And then, finally, were all of these patients with non-hemorrhagic strokes treated with resumption of anticoagulation?

DR. STEIN: Actually, they were not. We did not attempt to adjudicate either through our CEC or ask the sites specifically to adjudicate mechanism of the stroke. I think for clear reasons, that's very difficult, particularly retrospectively. But for a couple of those new ischemic strokes, the impression at the treating site was that they were

non-cardioembolic in origin and they were treated with antiplatelet agents and not with resumption of warfarin.

DR. BRINKER: Thank you.

DR. PAGE: May I follow up on Dr. Brinker's question? You showed a beautiful set of echo images of the thrombus in the appendage that then broke out and then potentially could cause a stroke. But after it causes a stroke, it's no longer in the appendage. So obviously if there was a clot at one site or another in the heart, on or around the device, if it had already caused a stroke, it might be gone and no longer be visible.

Do you have any data in terms of routine TEE, when someone hasn't had a TIA or a stroke, that gives an idea of how often thrombus is seen in the un-anticoagulated patients with the occluded device?

DR. STEIN: Yes, we do, and I'm going to invite Dr. Reddy up to address the issue of device thrombus. As he does, I think your fundamental point about this adjudication issue really gets to why in our view it's necessary to look at all stroke. And again, you know, as useful as it can be to try to break down by mechanism, we sort of get out of some of these adjudication issues by focusing on what is relevant to patients, which is just is there or isn't there a stroke? But in terms of specifically addressing the question about thrombus, let me ask Dr. Reddy to deal with that.

DR. PAGE: And I've got to just warn you, we will be asking about particulars related to stroke. We understand your point, that you prefer us to look at all strokes, but it's our job to look at individual stroke events and what the etiology might be. So please indulge us in that.

Dr. Reddy.

DR. REDDY: Thank you. Vivek Reddy, Mount Sinai Hospital.

As I bring this up -- here it is. I certainly think you're right. The fact is we don't know whether it's with the WATCHMAN device or when a patient is on oral anticoagulation, what the mechanism of stroke is when they still have a stroke. But here is some data. I think it's a nice dataset because it includes all of the three major trials where we have this data, and what you're looking at is the incidence of device-related thrombus, so thrombus on the face of the device identified by routine TEE imaging. So, if you look across the top, you'll see that there is thrombus, some ranging anywhere between 2.2% to 6.0% of the patients. So around 5% of the patients experienced thrombus sometime during this surveillance. Now --

DR. PAGE: I'm sorry to interrupt, Dr. Reddy, but just to be clear, that's asymptomatic thrombus? That is thrombus seen on echo?

DR. REDDY: So these are thrombi -- the majority of these are asymptomatic. If you follow down, you can see that a small percentage -- well, if you look at the numbers, two of the patients in PROTECT, one in CAP, and one in PREVAIL had an associated ischemic event as a result -- an ischemic stroke event as a result of having the thrombus. So, if you look at the annualized device thrombus-related stroke, you see it's somewhere around 0.1%. So device-related thrombus does occur, but using routine surveillance, identifying with TEE, giving these patients a month or so of additional anticoagulation seems to be an acceptable strategy to keep the associated embolism and stroke rate to a very low level.

DR. PAGE: Okay. And, again, I don't want to dominate, but I just want to understand. So, if you could put the slide back up, please.

DR. REDDY: It's just coming up. One second.

DR. PAGE: If I read it correctly, in PROTECT there were 4%, and in PREVAIL, 6% of subjects. If they just happened to have a TEE, there's stroke --

DR. REDDY: Well, it's not just --

DR. PAGE: -- there's a thrombus there?

DR. REDDY: Right. So it has not just happened. Remember, all of these patients are mandated to have TEE at 45 days, potentially at 6 months depending on what the 45-day looks like, and again at a year.

DR. PAGE: Okay.

DR. REDDY: And so during this time this was what was identified.

DR. PAGE: And once they had been cleared and they're on chronic therapy, were there any routine TEE data?

DR. REDDY: Beyond that point, no.

DR. PAGE: Okay.

DR. REDDY: But I do again want to point out, when I showed you the ischemic stroke rates, long term, which we have from PROTECT and CAP, we did not see a sudden increase in such events late.

DR. PAGE: I understand. Thank you very much.

Dr. Cigarroa and then Dr. Lange.

DR. CIGARROA: So the majority of that data then is populated by the protocol-mandated TEE at 45 days, correct?

DR. STEIN: By TEEs at 45 days, then again in two of the studies at 6 months, and

then in all of three of the studies that he showed you again at one year.

DR. CIGARROA: Great. The second question is the inclusion criteria included patients who may have previously had a neurologic event, either CVA or TIA.

DR. STEIN: Yes.

DR. CIGARROA: Do we know what percentage of patients who experienced an event during the trial had previously had a neurologic event, and is there any difference in the two arms?

DR. STEIN: Yeah. I can show you first the results of that subgroup analysis to show you that, in fact, there is no statistically important interaction in terms of primary efficacy when you look at those patients either who did or who did not have a prior history of TIA or stroke. And so again, you know, for the overall primary efficacy endpoint, stroke, all stroke, systemic embolism, or cardiovascular or unexplained death, for both groups the hazard ratios are to the left of 1 and the p for interaction is 0.62.

One thing that we do point out and that we've discussed interactively with FDA is instead of looking at this as hazard ratios, if you look at it as absolute event rates in both arms, WATCHMAN and warfarin, there is a higher risk of events in those who had a prior TIA or stroke. I think again, that's to be anticipated. That again goes with just the higher rate as CHA_2DS_2-VASc scores go up. But we do think it's important that that be included in the labeling and that that be a part of a benefit-risk discussion with patients should this device get approved.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: I'm trying to just get my hands wrapped around the death rate between the two groups and it looks like there were -- at least in the PREVAIL study there were eight deaths in the WATCHMAN group and six in the control group, and again, a 2:1 randomization. My understanding is that there were -- that the deaths in the WATCHMAN group were six sudden cardiac deaths and two MIs and in the control group it was five sudden deaths and one heart failure. That's my understanding, and I just wanted to get that corrected because it also looks like two people with hemorrhagic stroke died, but I don't see that. That's not sudden cardiac death.

So sometime over the break, just in the PREVAIL, if we could figure out what the death rate was and if we could look at all-cause mortality as well, because obviously cardiovascular death is important, but if people die of other reasons and can't die of cardiovascular death, that's important as well.

DR. STEIN: Yes, we can begin -- and I do think we don't have to wait for the break, if that's all right. I think we have the data. And so these are the causes of death in PREVAIL, again, the PREVAIL-only population. So, again, it's not the Bayesian analysis. These are just the specific PREVAIL subjects. And just as in PROTECT, there is an excess of death due to cardiovascular reasons, and if you look at the causes, again, it's a higher rate of death due to hemorrhagic stroke in the control group and likewise a higher rate of sudden unexplained death in the control group.

Now, I've got to admit to a bit of, maybe, a professional bias that I have. As an electrophysiologist, I look at sudden death, and I think it's arrhythmic. These were not due to documented arrhythmias. These were sudden unexpected death. And one of the things

that we think needs to be kept in consideration is the possibility that these may have been sudden deaths due to catastrophic internal bleeding events.

DR. LANGE: If somehow over the break -- because I want to look at the slide, because it looked like there are nine deaths in the WATCHMAN group. It's not a big deal, but I want to take a look, because it looks like -- unless somebody died twice.

(Laughter.)

DR. LANGE: There are slow deaths.

DR. PAGE: Just so I'm clear, Dr. Lange, can you restate your question?

DR. LANGE: On the last slide it looks like --

DR. STEIN: Yeah, we need to double-check the numbers on that last slide that we showed you --

DR. LANGE: Yeah, that would be great.

DR. STEIN: -- which we will absolutely do.

DR. LANGE: Thanks. There it looked like six died of sudden cardiac death, two died of MI, and one died of hemorrhagic stroke, which would be nine deaths. So, just for the record, we'll clarify that. Thanks.

DR. STEIN: Yes. And thank you for bringing that out.

DR. PAGE: Thank you.

We're nearing our break time at 10:00, but again, I want to get in whatever questions people might have, especially that might inform the investigation over the lunch break.

Dr. Brinker and then Dr. Noonan.

DR. BRINKER: Thank you.

This question pertains to patients who are having efforts to maintain rhythm rather than rate control. Number one, I assume that most of the experience has been in rate control patients in which there are no repeated attempts to maintain rhythm, whether that includes ablation or not. But assuming a patient comes -- and some have, as you suggested in your preamble -- for cardioversion and they have not been on any anticoagulation, is TEE recommended before cardioversion?

DR. STEIN: Yeah. Again, I want to try to answer maybe two different phases to the question, so specifically the one about cardioversion and then I'm going to ask Dr. Reddy to address some of the issues encountered around attempts to switch from a rate to a rhythm control strategy, particularly in the control arm of our trials.

We have limited experience with cardioversion in the trial. Our labeling does allow for cardioversion, and there were patients in the trials who did have cardioversions. I can show you the raw numbers. What we recommend with labeling is a TEE, I think, first -- again, to do surveillance for device-associated thrombus and also do surveillance for other non-LAA potential sources of thrombus. But, again, I think that may be overly conservative. But given again the data that we have, at least doing it that way appears to be safe.

DR. BRINKER: And post-cardioversion, is there a recommendation for a month or so of anticoagulation?

DR. STEIN: No.

DR. BRINKER: Or is that totality up to --

DR. STEIN: That's at the discretion of the physician. If the TEE is clear, we do not in

our labeling suggest that that is necessary.

DR. BRINKER: Thank you.

DR. STEIN: And in response to the question about other attempts at rhythm control, let me bring Dr. Reddy up.

DR. PAGE: And, Dr. Reddy, I'll ask you to keep this fairly concise. We will have opportunity to ask further questions.

DR. REDDY: Okay. I'll bring up the slide in just a second. With regard to the cardioversion, while there was no formal recommendation, that is what we did. We would continue for about a month.

Now, regarding ablations, this slide shows us, in PREVAIL, the number of actual ablations. Again, I just want to caution. Remember, the number of patients in PREVAIL alone are already small. The number of patients who underwent ablation is even smaller. It really is a fraction. But what you see if you look at the very bottom, 6.7% of the WATCHMAN patients underwent ablation sometime during follow-up; 12.3% of the warfarin patients.

I hope this answered your question.

DR. PAGE: Thank you.

Dr. Cigarroa and then Dr. Noonan.

DR. CIGARROA: Were there any observed late pericardial effusions or erosions, and if so, any concern of any excess risk in individuals with paroxysmal A-fib versus permanent?

DR. STEIN: There have been no late erosions or late pericardial effusions either in the clinical trial experience or in our commercial experience.

DR. PAGE: Thank you.

Dr. Noonan.

DR. NOONAN: Yes. Regarding Table -- or Slide Number 58, I'm trying to make that line up with some of these patient lists in the package you provided. I'm going to assume that Patient Number WM-2 corresponds to 8354001, a 79-year-old patient, pontine infarct. Let's assume that's due to posterior circulation disease. Then we can go on to the next patient, which is the thalamic infarct patient, Number 8. That patient we did have imaging for, and it was mostly posterior circulation disease and occluded right vertebral artery and so forth. So we're going to assume that maybe two of those patients had posterior circulation disease, unlikely due to emboli that may have originated from the heart because it's a long way there and it's a distal vessel.

So, if you excluded patients that have documented posterior circulation disease, probably not from the atrial appendage, how would it have changed the primary efficacy endpoints? I don't know if you can do that.

DR. STEIN: Yeah, we haven't done that analysis. Again, we did not prospectively adjudicate according to mechanism. By intention to treat, we are counting all strokes. And I think, you know, in terms of -- again, we're trying to be very conservative, I think, in terms of trying to decide how many of these patients we would retrospectively assign as having non-cardioembolic sources. We certainly can, if it's the request at the end of the break, exclude those two patients in particular as having no events and redo all the calculations if that's what you would like.

DR. PAGE: I don't know that a complete redo of the statistics is necessary, but I

think Dr. Noonan's point is important and worthy of our discussion later, as well as kind of education as an expert in the field, for the Panel, your perspective on how you would parse these out and whether you feel you can attribute them to a cardiac or non-cardiac source.

DR. NOONAN: Of course, you treat them with warfarin. Then you're going to treat both of the diseases at once.

DR. PAGE: I understand.

DR. STEIN: I'm wondering if I could just address that last comment --

DR. PAGE: Yes.

DR. STEIN: -- because I think this is something that came up at the last Panel as well, the issue of whether warfarin has pleiotropic effects beyond prevention of cardioembolic strokes. And there actually are recent data that address that. I'm going to ask Dr. Reddy, actually, to walk through that data.

DR. REDDY: Vivek Reddy, Mount Sinai.

I'll do this very quickly. I think the first is this slide. It's called the WARSS study. It looked at patients -- and this was a double-blind randomized trial that looked at patients who had sustained ischemic stroke and then were randomized to either warfarin or aspirin. And if I direct you to the next to the bottom line, the observed subsequent ischemic stroke rate was 17.8% in warfarin and 16% in the aspirin. So warfarin, at least in this study, didn't seem to confer any additional benefit over aspirin for non-cardioembolic stroke.

This slide is a very similar study. I'm going to pronounce this wrong. WASID, WASID, whatever -- the WASID study -- and it again looked at patients -- these are not AF patients again. These are patients who had a stroke for some reason other than AF presumably, and

again randomized to between either warfarin or aspirin. And if you look at the highlighted -- the bolder region next to the bottom, there was a similar rate between aspirin and warfarin. So the only point we're trying to make is that warfarin does not seem to confer additional benefit over an antiplatelet agent, like aspirin, for non-cardioembolic stroke.

DR. PAGE: Thank you.

We're at break time. Dr. Furie has a question, and if the other panelists don't have questions that we really need to address before lunchtime, then I'm going to call us at 10:00.

Dr. Furie, do you --

DR. FURIE: I can hold.

DR. PAGE: Okay, fine.

And, Dr. Brindis, your question won't hold?

DR. BRINDIS: One clarifying? You're the boss.

DR. PAGE: I am simply the Chair.

(Laughter.)

DR. PAGE: Please go ahead. We have 1 minute. Thank you.

DR. BRINDIS: All right. So Table 47 of your handout booklet. On page 107, it's just fuzzy math to me because it seems the focus of the new Panel is new data related to PREVAIL only, and that is the primary efficacy, warfarin, has 10. Yet the math, to me, adds up to nine. So maybe you can explain that in new events for the 2014 Panel. Table 47 on page 107 of your handout.

DR. STEIN: No. I think there are -- the primary efficacy event is all stroke, systemic

embolism, and cardiovascular death. So eight new ischemic strokes, one hemorrhagic stroke, and one death is how we get to 10. I think where there may be some confusion is that there were six individual endpoint component events in the warfarin group, but it only totals up to five primary efficacy events in this table because one of those was preceded by a hemorrhagic stroke. So the primary efficacy is time-to-first-event analysis, so that's why there's that -- where there's that mismatch in this table.

Now, I'd also like to pull up the table that we showed here, just to make sure that we avoid any confusion. In re-reviewing the CEC adjudications in preparation for this Panel, there was one WATCHMAN patient who had a hemorrhagic stroke that was followed by death. The CEC had not initially adjudicated that as a cardiovascular death. This was a WATCHMAN patient. We were actually uncomfortable with that adjudication, and we asked the CEC to re-adjudicate it, and they did re-adjudicate that as a cardiovascular death following a hemorrhagic stroke.

And so that's why the number of deaths that we showed today, and that we used for all of our analyses today, actually shows one more in the WATCHMAN arm than you saw in the table in your Panel pack. And I hope that that resolves the confusion. And I do believe that it is most accurate to go with that re-adjudication and the numbers that we used for our calculations today.

DR. PAGE: Thank you very much.

We're now going to take a 13-minute break.

(Laughter.)

DR. PAGE: Panel members, please do not discuss the meeting topic during the break

amongst yourselves or with any other member of the audience. We will resume promptly at 10:15. Thank you.

(Off the record.)

(On the record.)

DR. PAGE: Okay, it's now 10:15, and I'd like to call the meeting back to order. We'll now proceed with the FDA presentation. I invite the FDA representatives to approach the podium, and we have 90 minutes to present.

Welcome.

DR. NEUBRANDER: Thank you. Good morning, Dr. Page and members of the Panel. This is FDA's presentation on the WATCHMAN left atrial appendage closure, or LAAC, technology or WATCHMAN device, PMA Number P130013.

My name is Rachel Neubrander. I am a biomedical engineer in the Division of Cardiovascular Devices, and I'm the lead reviewer for this PMA.

I'd like to introduce the FDA review team members. They are myself, Dr. Andrew Farb, Dr. Manuela Buzoianu, and Dr. George Aggrey.

For our presentation today, I will first present introductory slides. Dr. Farb will then give the clinical presentation, and Dr. Buzoianu will give the statistical presentation. I will then present a brief summary.

The WATCHMAN LAAC technology, which I will refer to from here on as the WATCHMAN device, includes three components. The WATCHMAN implant itself, shown here on the right side of the slide, is available in five sizes. The 12 French delivery system and the 14 French access system are used together to deliver the implant to the left atrial

appendage. The Sponsor has performed all appropriate nonclinical testing, and this testing is complete.

The indications for use proposed by the Sponsor are as follows:

"The WATCHMAN LAAC Device is indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism."

This statement is largely the same as that presented at the December 2013 Panel meeting, with a slight change to the wording from patients who are eligible for warfarin therapy to patients who would be recommended for warfarin therapy, as highlighted on this slide. Dr. Farb will also provide some additional comments on the indications for use statement during his portion of the presentation.

Regarding regulatory history, FDA approved the PROTECT AF pivotal study for the WATCHMAN device in December 2005. PROTECT AF was a prospective randomized controlled trial to evaluate the safety and effectiveness of the WATCHMAN device for the prevention of ischemic stroke and systemic thromboembolism in subjects with non-valvular atrial fibrillation who are eligible for warfarin therapy. The study was designed to demonstrate non-inferiority of the WATCHMAN device plus 45 days of warfarin therapy to chronic warfarin therapy. A 2:1 randomization with two device subjects to one control subject was used. FDA subsequently approved the PROTECT AF continued access registry, or CAP, in 2008, and an original premarket approval application, or PMA, was submitted in 2008 as well.

The 2008 original PMA contained data collected in PROTECT AF and was discussed at a meeting of the Circulatory System Devices Panel held on April 23rd, 2009. At this meeting FDA raised concerns over the potentially confounding effects of concomitant antithrombotic use and the fact that a large percentage of subjects did not receive their assigned treatment in both the device and control groups. FDA also expressed concern at the number of acute procedure-related safety events that occurred during the study, particularly pericardial effusion and air embolism.

The Panel voted 7 to 5 in favor of approval with conditions. And while the Panel largely felt short-term effectiveness had been demonstrated by the data available from the PROTECT AF trial, the Panel believed that long-term effectiveness had not been adequately demonstrated. There were also varied opinions among Panel members on whether there was adequate information regarding the safety of the WATCHMAN device. Discussion ranged from the potential for improved safety compared to long-term warfarin use to concerns about the periprocedural risks associated with device placement.

After carefully considering the comments from the Advisory Panel and the split Panel vote, FDA issued a Not Approvable letter for the PMA on March 10th, 2010, based on the concerns presented and discussed at the Panel meeting. In the letter, FDA requested that the Sponsor perform a new study to provide evidence of safety and effectiveness of the WATCHMAN device and worked interactively with the Sponsor to design this new study, which was named PREVAIL, and this was approved in 2010.

PREVAIL was designed to address the limitations of PROTECT AF that led FDA to issue the Not Approvable letter. But because FDA and the Sponsor agreed that there was some

value in the data from PROTECT AF, PREVAIL was also designed to build on that existing data by incorporating a portion of the PROTECT AF data into the PREVAIL statistical analysis. In addition, although continued follow-up from PROTECT AF and CAP would not be sufficient on its own to support approval, FDA and the Sponsor agreed that the Sponsor should continue to collect follow-up data on subjects enrolled in PROTECT AF and CAP, to collect important long-term safety and effectiveness data that would supplement the data collected in PREVAIL.

The limitations of PROTECT AF that were addressed in PREVAIL include the inclusion of low-risk patients, the potential confounding effect of concomitant clopidogrel use, and warfarin compliance and monitoring. Dr. Farb will discuss further the PREVAIL trial design and how the limitations of PROTECT AF were addressed.

Finally, a second PMA, P130013, was submitted and was discussed at the December 2013 Panel meeting. This PMA included the results of PREVAIL based on a January 2013 dataset which included an average of 11.8 months of follow-up as well as long-term data from PROTECT AF and CAP.

As a brief reminder of the PREVAIL results that were discussed at the December 2013 Panel meeting, the WATCHMAN device did not meet non-inferiority compared to warfarin for the PREVAIL first primary endpoint, which was the composite of all stroke, systemic embolism, and cardiovascular or unexplained death. And for the PREVAIL-only cohort, the event rates for the individual components of the first primary endpoint all favored the control group.

The WATCHMAN device did meet non-inferiority compared to warfarin for the

PREVAIL second primary endpoint, which was the composite of ischemic stroke and systemic embolism occurring after 7 days post-randomization, and also met the performance goal for the implant procedure-associated major event rate, which was the PREVAIL third primary endpoint. In addition, WATCHMAN device implantation was not associated with a signal of reduced overall bleeding events.

Evaluation of new operators and new sites in PREVAIL indicated that new operators were able to successfully and safely implant the device at rates comparable to experienced operators, and that there was an acceptable operator learning curve associated with device implantation.

At the December 2013 Panel meeting, the Panel voted 13 to 1 in favor of device safety, effectiveness, and benefit-risk profile. After the December 2013 Panel meeting, FDA received updated information that included a significant amount of additional follow-up in PREVAIL. The updated PREVAIL dataset revealed an imbalance in the ischemic stroke rate between the WATCHMAN and control groups, with a total of 13 events in the WATCHMAN group and 1 event in the control group. Even accounting for the 2:1 randomization, this imbalance raised concerns regarding device effectiveness.

Finally, the overarching question the FDA would like the Panel to keep in mind is whether the totality of the data that are presented today changed the previous conclusion that there is a favorable benefit-risk profile for the WATCHMAN device.

I'd like to now turn things over to Dr. Farb, who will present FDA's clinical presentation.

DR. FARB: Thank you. And good morning, Dr. Page and members of the Advisory

Panel. I'm Andrew Farb, a cardiologist and medical officer in the Division of Cardiovascular Devices, and I'll be presenting FDA's clinical review.

Here is an outline of my presentation. I'll start with a brief overview of the PREVAIL trial, followed by a discussion of the updated events in the PREVAIL-only dataset and their impact on the first and second primary endpoints. Then I'll present the WATCHMAN device randomized trial data within a benefit-risk framework, followed by a return to the indication for use statement before closing remarks.

The definitions of these terms are important as we go forward. PREVAIL only refers to analyses based on data limited to new subjects enrolled in the PREVAIL trial. In contrast, PREVAIL or PREVAIL Bayesian analyses are based on data that include new subjects enrolled in the PREVAIL trial plus PROTECT trial data down-weighted by 50%.

Let's briefly review the original PREVAIL trial. The PREVAIL trial was needed and designed to address the limitations of the PROTECT AF study, and it does so by enrolling high-risk subjects, that is, those with $CHADS_2$ scores of at least 2 or a $CHADS_2$ score equal to 1 with additional stroke risk factors. It excluded subjects indicated for chronic clopidogrel therapy to reduce confounding of ischemic versus hemorrhagic events. It provided for enhanced monitoring of warfarin use to increase compliance and INR control, and it reduced a non-inferiority margin from 2.0 to 1.75 for the first primary endpoint.

PREVAIL also added a secondary primary endpoint to address LAA occlusion proof of concept to prevent ischemic stroke and systemic embolism and added a third primary endpoint to address device implantation safety concerns. It also required participation of new operators to address the device implantation learning curve.

The foregoing concerns with the PROTECT AF trial precluded approval of the WATCHMAN device following the first Advisory Panel meeting in 2009. Nonetheless, FDA recognized that despite study limitations, there was value in the PROTECT data. The FDA and the Sponsor collaboratively developed a Bayesian study design for PREVAIL, in which a portion of the PROTECT data would be used as an informative prior. Importantly, the FDA and the Sponsor agreed up front in designing PREVAIL that prior PROTECT data would be discounted 50% in the analysis of the first and second primary endpoints.

The objective of PREVAIL was to demonstrate the safety and effectiveness of the WATCHMAN device for the prevention of ischemic stroke and systemic embolism in subjects with non-valvular AF who are eligible for warfarin therapy. The control group was treated with adjusted dose warfarin, and subjects were randomized in a 2:1 fashion to the WATCHMAN group or to the warfarin control group. The statistical analyses of the first and second primary endpoints were designed to include prior data from PROTECT down-weighted 50%.

It's important to review the differences in the anticoagulation and antiplatelet strategies between the WATCHMAN group and the warfarin group. Post-WATCHMAN implantation, subjects were to receive adjusted dose warfarin plus aspirin. At 45 days post-procedure, if the TEE demonstrated adequate LAA occlusion, warfarin could be discontinued. Subjects who discontinued warfarin were treated with dual antiplatelet therapy through 6 months. Clopidogrel was to be stopped at 6 months post-device implantation and aspirin was to be continued indefinitely so that beyond 6 months, in what could be considered destination therapy, we are essentially comparing two treatment

strategies, the WATCHMAN device plus aspirin versus warfarin therapy. That's why the true effect of this, of the WATCHMAN device, is best understood when WATCHMAN subjects are on aspirin alone during follow-up. In control subjects, adjusted dose warfarin to achieve a target INR of 2.0 to 3.0 was to be administered for the duration of the trial.

This slide shows how the conduct of the PREVAIL trial addressed the limitations of PROTECT AF and was necessary. Among subjects randomized to the WATCHMAN group, there was a lower rate of subjects who did not receive the device in PREVAIL (3.6%) versus PROTECT (11.9%). There was a higher rate of warfarin discontinuation in WATCHMAN subjects in PREVAIL at 45 days (92% versus 87%) and at 6 months (98% versus 92%). And there was a lower rate of long-term warfarin resumption in PREVAIL (4.8%) compared to PROTECT (7.1%).

These improvements in trial execution are important to enhance the robustness of study results, because the more the two treatment groups resemble each other, that is, by WATCHMAN subjects remaining on warfarin, the easier it is to pass a non-inferiority test comparing the device and the control. For the control group, there was a high rate of documented compliance with monthly INR monitoring in PREVAIL, and there were no control subjects who never started anticoagulation in PREVAIL.

As designed, the mean $CHADS_2$ and CHA_2DS_2-VASc scores were higher among the new PREVAIL subjects versus the prior PROTECT subjects. This is also important when considering the effectiveness of the WATCHMAN device in the high-risk subjects enrolled in PREVAIL.

Turning to the PREVAIL-only data, based on the database lock in January of 2013 and

presented at the December 2013 Panel, notable is the number of events and rate differences for ischemic stroke plus systemic embolism between the WATCHMAN and control groups. The rate of ischemic stroke was 1.94 in the WATCHMAN group versus 0.71 in the controls. The rates of the other events also favored the warfarin group.

Based on the database lock in January 2013, for the first primary endpoint of all stroke, systemic embolism, or cardiovascular or unexplained death, the 18th-month event rates were similar between the groups. However, the WATCHMAN group failed the non-inferiority test for the first primary endpoint.

Here are the results from the Bayesian analysis of the second primary endpoint, the rates of ischemic stroke or systemic embolism after the first 7 days post-randomization. The 18th-month event rate was lower in the control group, but the WATCHMAN event rate just met non-inferiority versus warfarin for the second primary endpoint based on the upper bound of the rate difference between groups.

So, in the January 2013 dataset presented at the last Panel meeting, the ischemic stroke rate numerically favored the control group in the PREVAIL-only dataset, which was consistent with the results of PROTECT. And in the Bayesian analysis of PREVAIL, non-inferiority for the first primary endpoint was not met and non-inferiority for the second primary endpoint was met for the risk difference.

There are important caveats to consider regarding the January 2013 PREVAIL dataset regarding the PREVAIL-only subjects. The mean duration of follow-up from the time of randomization was only 11.8 months, and only 28% of subjects had reached or passed the 18th-month follow-up window.

As you have heard, in response to FDA's request for updated study data following the December 2013 Panel meeting, the Sponsor provided information on new events. What's most notable and most relevant to the WATCHMAN device is the eight new ischemic strokes that were reported in the device group between the January 2013 dataset lock and the June 2014 dataset lock.

The next series of slides will show how the PREVAIL-only dataset has evolved since the December 2013 Panel meeting. Recall that the mean duration of subject follow-up in January of 2013 was only 11.8 months. This increased to 25.9 months in the June 2014 dataset. Moreover, only 28% of PREVAIL-only subjects had reached or passed 18 months of follow-up in the January 2013 dataset, which increased to 100% in the June 2014 dataset.

The PREVAIL-only total patient-year follow-up also increased substantially from January 2013 to June 2014, from 396 patient-years to 860 patient-years. What this means is that although the PREVAIL-only data were not powered to stand alone, the study now carries much more weight in considering the totality of the WATCHMAN device safety and effectiveness information.

Clearly, the reason we are here today involves the new ischemic strokes in the WATCHMAN group, which has led to a reassessment of the benefit-risk profile of the WATCHMAN device compared to warfarin. On top of the original 5 ischemic strokes, there were 8 new ischemic strokes for a total of 13 in the WATCHMAN group versus a total of only 1 ischemic stroke in the control group and no new events in the interim 18 months, a significant imbalance even when accounting for the 2:1 device-to-control randomization scheme.

After incorporating the new events, the ischemic stroke rate in the WATCHMAN group and the PREVAIL-only dataset increased from 1.94 to 2.3, while the rate in the control group decreased from 0.71 to 0.34. The rate of ischemic strokes in the WATCHMAN group is nearly 15 times greater than the rate in the control.

Next, we'll look at the impact of these new events on the Bayesian analysis of PREVAIL's first and second primary endpoints. Recall that for the first primary endpoint of all stroke, systemic embolism, or cardiovascular or unexplained death, the 18th-month rates were similar in the January 2013 dataset, but the WATCHMAN device failed the non-inferiority test.

With data added through June of 2014, the WATCHMAN event rate remained about the same and the control rate decreased. As a result, the rate ratio increased in favor of the control group, and the upper bound of the credible interval also increased from 1.89 to 2.05. The 2.05 upper bound exceeded the non-inferiority success criterion by a larger amount so that the WATCHMAN device rate moved further away from meeting non-inferiority in the updated data.

Next, the second primary endpoint of ischemic stroke or systemic embolism occurring after the first 7 days post-randomization. Recall that in the January 2013 dataset, the 18th-month event rate was lower in the control group, but the upper bound of the credible interval of the rate difference was less than the non-inferiority margin, so that the WATCHMAN device met the non-inferiority endpoint.

With added data through June of 2014, the 18th-month rate increased in the WATCHMAN group from 0.0253 to 0.0294, which is important when considering device

effectiveness, and the event rate decreased in the control group. The rate difference increased in favor of the control group, as did the upper bound of the credible interval. The upper bound now exceeded the non-inferiority success criterion so that the WATCHMAN device was no longer non-inferior to warfarin for the second primary endpoint.

Thus, for the updated PREVAIL first and second primary endpoint results, the WATCHMAN device did not meet non-inferiority versus warfarin for all stroke, systemic embolism, or cardiovascular or unexplained death, or for stroke or systemic embolism excluding the first 7 days post-randomization. Since the PREVAIL Bayesian analysis includes both PREVAIL-only data and a substantial portion of PROTECT data, the failure to meet non-inferiority for both of these endpoints should be carefully considered in assessing the totality of the WATCHMAN outcomes.

In the next portion of the clinical review, I'll focus on benefit-risk considerations. These questions are intended to frame important benefit-risk issues that would be applicable to physicians in their conversations with patients regarding the use of the WATCHMAN device:

- First: Is implantation of the WATCHMAN associated with an acceptable rate of procedure-related complications?
- Next: Does the WATCHMAN provide adequate protection from ischemic stroke or systemic embolism in at-risk atrial fibrillation patients?
- Third: Is the avoidance of long-term warfarin following implantation of the WATCHMAN associated with a reduced risk of hemorrhagic stroke?
- Fourth: Is there a signal of a reduced rate of cardiovascular or unexplained

death in patients treated with the WATCHMAN device?

- Fifth: Is there a signal of reduced bleeding complications in patients treated with the WATCHMAN device?

For Question 1 that deals with the safety of the WATCHMAN implant procedure, this was addressed at the December 2013 Panel meeting. The third primary endpoint of procedural safety was met and new operators were able to implant the device successfully and safely, reflecting an acceptable learning curve.

Next, the critically important question of whether the WATCHMAN device provides adequate protection from ischemic stroke or systemic embolism in at-risk AF patients. Starting with PROTECT AF, the rates of ischemic stroke or systemic embolism, measured in events per 100 patient-years, numerically favored the control group. The rate was 36% higher in the WATCHMAN group. The proportion of subjects with events tells a similar story, numerically in favor of the control group. The rate was 37% higher in the WATCHMAN group.

This Kaplan-Meier curve for freedom from ischemic stroke or systemic embolism shows the WATCHMAN line below the control line, but there is substantial overlap in the 95% confidence intervals.

Shifting to the PREVAIL-only dataset, there is greater than a sevenfold disparity in the rates of ischemic stroke or systemic embolism that are strongly in favor of the control group. Similarly, there was an approximately sevenfold higher proportion of subjects with ischemic stroke or systemic embolism events in the WATCHMAN group versus the control group.

Applying the Bayesian model with a non-informative prior to the 18-month ischemic stroke or systemic embolism rates, one can see the low rates in the control group versus the WATCHMAN group with non-overlapping credible intervals.

The difference in the ischemic stroke or systemic embolism rate is depicted on this K-M plot, showing that the curves separate over time. The log-rank test p-value is in favor of the control group, and that reflects a measure of the separation between the curves. And one should be mindful of the second primary endpoint in PREVAIL, which is ischemic stroke or systemic embolism occurring after the first 7 days post-randomization, so it does not include periprocedural events. Recall that the WATCHMAN device failed the non-inferiority test versus warfarin. So the issue has been raised of whether the low rates of ischemic stroke or systemic embolism in the PREVAIL-only group might be explained by over-performance of that group.

Here are the ischemic stroke rates in the warfarin groups of contemporary anticoagulation trials, to which we have added PROTECT, PREVAIL only, and the agreed-upon 50% weighted PROTECT plus PREVAIL data. You can see that the rate of ischemic stroke in the warfarin group of the 50% weighted PROTECT plus PREVAIL is closer to the other contemporary anticoagulation trials compared to the PREVAIL-only rate.

On this slide we present the 95% confidence intervals around the point estimates for ischemic stroke. The confidence intervals from the 50% weighted PROTECT data plus PREVAIL overlaps with the contemporary anticoagulation trials.

In this slide we have added the WATCHMAN device group ischemic stroke rates from PREVAIL only and the 50% weighted PROTECT plus PREVAIL data. Note that the higher

ischemic stroke rates in the 50% weighted PROTECT plus PREVAIL group in the WATCHMAN device subjects has little, if any, overlap with the confidence intervals in the contemporary anticoagulation trials.

So, regarding the performance of the PREVAIL-only warfarin group, the reasons for the lower than expected ischemic stroke rates are not apparent, but conclusions drawn from comparisons across different trials should be made cautiously and are limited by known and unknown differences in patient populations and trial execution.

PREVAIL was a well-monitored, well-executed randomized trial. It's possible that enhanced anticoagulation management and treatment of risk factors such as hypertension and lipids contributed to the low ischemic stroke rate, but this is uncertain. One should also consider the second primary endpoint results in PREVAIL, where non-inferiority was not met, which included the agreed-upon portion of PROTECT data in the analysis.

So back to the benefit-risk question of whether the WATCHMAN device provides adequate protection from ischemic stroke or systemic embolism in at-risk AF patients. With an additional 18 months of follow-up, the rate of ischemic stroke or systemic embolism strongly favored the control group in PREVAIL, in the PREVAIL-only data. The rate of ischemic stroke or systemic embolism numerically favored the control group in PROTECT AF. In the PREVAIL Bayesian analysis, the WATCHMAN group did not meet non-inferiority for the second primary endpoint of ischemic stroke or systemic embolism occurring greater than 7 days post-randomization.

Next, is the avoidance of long-term warfarin following implantation of the WATCHMAN device associated with a reduced risk of hemorrhagic stroke? Here are the

hemorrhagic stroke rates in PROTECT and PREVAIL only, and what's notable is the disparity in the events are strongly in favor of the WATCHMAN group in PROTECT: 0.2 per 100 patient-years in the device subjects versus 1.1 in controls.

The next series of slides will focus on the PROTECT trial, since here is where the hemorrhagic stroke rate difference was most marked. And, more specifically, I'm going to focus on the 10 hemorrhagic stroke events in the PROTECT warfarin control group, posing the question of the whether the signal of protection from hemorrhagic stroke afforded by the WATCHMAN device versus warfarin is robust.

First, here are the hemorrhagic stroke rates from contemporary anticoagulation trials, to which we have added the PROTECT hemorrhagic stroke that is greater than twofold higher than the other studies. There is no reason to believe that the PROTECT warfarin subjects were at greater than two times higher risk than the subjects in the other trials. Further, with 95% confidence intervals added, note the absence of overlap of the PROTECT warfarin group compared to most of the other anticoagulation trials.

The higher than expected rate of hemorrhagic stroke in the PROTECT warfarin subjects compared to other individual anticoagulation studies was also consistent with the meta-analysis of studies of Coumadin derivative use versus aspirin.

The next series of slides reflect a detailed review of the subject narrative summaries of the 10 subjects with hemorrhagic strokes in the PROTECT control group. While appropriately accounted in an ITT analysis, one subject was off warfarin for over 38 months at the time of the event and was taking aspirin alone, and one of the subjects had no CNS imaging performed. The patient was adjudicated as having a hemorrhagic stroke, even

though the protocol definition of hemorrhagic stroke requires CT or MRI confirmation.

There was also the issue of potential inflation of the hemorrhagic stroke rate in warfarin subjects by the concomitant use of antiplatelet agents. Of the 10 PROTECT control subjects with hemorrhagic stroke, four were taking aspirin at the time of the event, and antiplatelet use information was not available in one additional subject.

It should be noted that professional society guidelines state that the addition of aspirin to anticoagulation in stable vascular disease patients offers no benefit and increases the risk of bleeding, including intracranial hemorrhage, and concomitant antiplatelet therapy should not be prescribed in the absence of a subsequent cardiovascular event. One could postulate that more appropriate and judicious use of aspirin in patients with stable vascular disease would have been associated with a reduced risk of hemorrhagic stroke.

Next is the issue of hemorrhagic stroke and/or cranial bleeds and the challenges of adjudicating events. Of the 10 PROTECT control group subjects with hemorrhagic strokes, five events that occurred following falls were adjudicated as hemorrhagic stroke. Of these, four were associated with subdural hematomas, one of which also had intracerebral bleeding in a subject on aspirin alone, and one had subarachnoid hemorrhage. Two subjects hit their head, one fell down the steps, and information is lacking on the other two. There was concomitant use of antiplatelet agents in at least two of the four subjects taking warfarin.

However, falls resulting in subdural hematoma were not unique to the control group in PROTECT. For example, three WATCHMAN subjects fell, resulting in subdural hematomas. Two were on aspirin alone, and one was on aspirin plus warfarin. In contrast

to the warfarin subjects, these WATCHMAN subjects were not adjudicated as having hemorrhagic stroke.

When one considers cranial bleeds in addition to hemorrhagic strokes, the difference between the WATCHMAN and control groups is less pronounced, with 8 versus 11 hemorrhagic strokes plus cranial bleeding events compared to 3 versus 10 hemorrhagic stroke events, respectively.

So, in evaluating whether hemorrhagic stroke reduction afforded by the WATCHMAN device versus warfarin is a robust benefit, one should note that the control group hemorrhagic stroke rate was greater than twofold higher than the rates reported in other contemporary oral anticoagulation trials. We acknowledge that conclusions drawn from comparisons across different trials should be made cautiously.

Of the 10 control group events, one subject was not using warfarin and one subject had no confirmatory CNS imaging. The concomitant use of antiplatelet agents in several subjects could have inflated the hemorrhagic stroke rate. There are potential adjudication challenges in subjects with cranial bleeds associated with head trauma. And, lastly, a signal of reduced hemorrhagic stroke risk in WATCHMAN subjects versus controls has not been observed in the PREVAIL-only dataset.

Next, is there a signal of a reduced rate of cardiovascular or unexplained deaths in patients treated with the WATCHMAN device? The rates of these events numerically favored the WATCHMAN groups in both PROTECT and PREVAIL only.

In considering the potential association or even causality between the WATCHMAN device or warfarin on cardiovascular or unexplained death, one should be mindful of the

clinical characteristics of the enrolled subjects. Recall that the WATCHMAN studies enrolled a predominantly elderly population with a high frequency of important cardiovascular comorbidities, including coronary atherosclerosis, hypertension, and dyslipidemia. Also MI, coronary revascularization procedures, heart failure, pacemakers or ICDs, prior stroke, and diabetes were common.

In PROTECT, most cardiovascular or unexplained deaths were sudden or due to cardiac or coronary disease, and among the sudden deaths, patients had documented comorbidities such as coronary atherosclerosis, prior MI, LV dysfunction, heart failure, ICDs, and heart valve disease. This pattern was the same for PREVAIL, with sudden deaths comprising the majority of events in subjects with known cardiovascular comorbidities along with acute MI and heart failure.

So when considering the observed reduced rate of cardiovascular or unexplained death in WATCHMAN subjects, fatal non-stroke and non-cranial bleeding events are counted towards the primary endpoint in PROTECT and PREVAIL but were not causally associated with warfarin use in the control group, the WATCHMAN device, or the WATCHMAN device implant procedure. So these events should be viewed as adding more noise than signal. And although mortality rate differences that include stroke-related deaths favor the WATCHMAN group in PROTECT AF, the difference is driven by events adjudicated as hemorrhagic strokes, which has been previously discussed.

Finally, is there a signal of reduced bleeding complications due to the avoidance of long-term anticoagulation in patients treated with the WATCHMAN device? Reduction in the rate of bleeding complications associated with the use of anticoagulants is a potential

advantage of the WATCHMAN. In the WATCHMAN trials, it's important to understand that major bleeding was defined as events adjudicated as serious adverse events; that is, a bleeding scale, such as the GUSTO or TIMI scale, was not used.

Here is a table of major bleeding events in PROTECT, stratified by the timing of events. There is an apparent tradeoff between upfront procedure-related bleeding in the WATCHMAN group versus later bleeding in the control group, but the overall major bleeding rates were similar between the two treatment groups. A similar pattern was seen in PREVAIL only, a tradeoff between procedure-related and later bleeding events, so that the overall major bleeding rates were similar between the treatment groups in PREVAIL as well.

There are additional caveats to consider when assessing major bleeding events. In PROTECT, at least 5 of the 19 control subjects were taking antiplatelet agents in addition to an anticoagulant at the time of the event, and in 8 other subjects that were taking aspirin at the time of study enrollment, the narratives are unclear whether the subject was still taking aspirin at the time of the bleeding event. In the PREVAIL-only dataset, 10 of 16 control subjects were taking aspirin in addition to an anticoagulant at the time of the bleed.

So, to address the benefit-risk question around major bleeding, neither PROTECT nor PREVAIL showed a reduction in overall major bleeding rates between the WATCHMAN and control groups. There was a signal of a reduced rate of late major bleeding in the WATCHMAN group, which can be viewed as an expected finding due to lower intensity antithrombotic therapy in WATCHMAN subjects versus controls. Concomitant use of aspirin with warfarin may have increased the bleeding risk in the control group.

The HAS-BLED scoring system has been used to assess major bleeding risk in patients taking oral anticoagulation therapy. But as you have seen, it's important to recognize that there is overlap in the HAS-BLED risk factors for major bleeding with the $CHADS_2$ risk factors for stroke in AF patients. And similar overlap is seen with the CHA_2DS_2-VASc scoring system, so that in considering benefit-risk, patients at increased risk for bleeding are often at increased risk for stroke.

In thinking about HAS-BLED scores in the context of the WATCHMAN program, HAS-BLED scores were not prospectively collected in the WATCHMAN studies, and there was no subgroup analysis of outcomes stratified by HAS-BLED score to identify a patient cohort that derived an enhanced benefit for the WATCHMAN device. Further, there are no studies evaluating the benefit-risk profile of the WATCHMAN device versus alternative therapies in high HAS-BLED score patients.

To turn to the elements of benefit-risk, the Sponsor has performed a patient-level meta-analysis of the PROTECT and PREVAIL-only subjects, but does pooling in such a manner provide a completely accurate picture of benefit-risk?

Here is FDA's analysis that looks at these endpoint events stratified by the two individual studies, PROTECT and PREVAIL only. There are apparent differences between PROTECT and PREVAIL-only outcomes for all stroke or all stroke plus systemic embolism or ischemic stroke plus systemic embolism, in favor of the control group, while the hemorrhagic stroke hazard ratio favored the WATCHMAN group.

So regarding the Sponsor's patient-level meta-analysis, the analysis pools results from just two trials, PROTECT and PREVAIL, rather than using the usual practice of

aggregating data from many independent studies. PROTECT and PREVAIL only had divergent results with respect to hemorrhagic versus ischemic stroke. The interpretation of the Sponsor's meta-analysis is limited by a substantial difference in patient follow-up and a lack of covariate adjustment. Also, recall that in the design of PREVAIL there was upfront agreement between the Sponsor and FDA that because of study execution issues, the PROTECT AF data would be down-weighted 50%, and the WATCHMAN device failed the non-inferiority test for both the first and second primary endpoints.

The FDA also has comments on the imputed placebo analysis, which supports the postulate that the WATCHMAN device is better than no treatment or ineffective treatment, that is, aspirin. This analysis acknowledges that warfarin is superior to WATCHMAN for ischemic stroke prevention. The estimates for ischemic stroke risk using analysis of baseline $CHADS_2$ and CHA_2DS_2-VASc scores and the robustness of the conclusions drawn from the statistical comparison across different trials is limited. Importantly, there are no randomized trials comparing the WATCHMAN device to no therapy or antiplatelet therapy.

The final topic involves the language in the indications for use statement, which was presented earlier. The sentence in blue deserves further discussion, that "The device may be considered in patients with non-valvular AF who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism."

How should this sentence be interpreted? The WATCHMAN device may be considered in patients at risk for stroke for whom warfarin would be recommended. The language is specific to warfarin. It does not -- is specific to patients recommended for

warfarin. It does not apply to patients for whom a NOAC would be recommended, since the safety and effectiveness of the WATCHMAN device has not been compared to any of the NOACs. It does not apply to patients with absolute relative contraindication to oral anticoagulation, since the safety and effectiveness of the WATCHMAN device has not been compared to no therapy or antiplatelet therapy.

To conclude, despite a proven highly favorable benefit-risk profile, oral anticoagulation is underutilized in AF patients who had increased risk for ischemic stroke and systemic embolism, primarily due to concerns about bleeding complications.

If thromboembolism from the LAA is the predominant mechanism for ischemic stroke and systemic embolism, interventions that occlude the left atrial appendage orifice might offer an alternative to anticoagulation.

The PROTECT AF trial showed the potential utility of the WATCHMAN device but was not adequate for FDA approval, and a second trial was needed.

The PREVAIL trial was developed to address the limitations of the PROTECT AF study and efficiently collect additional safety and effectiveness data of the WATCHMAN device.

The FDA and the Sponsor reached consensus on the design elements of PREVAIL, particularly the use of prior data from PROTECT AF, which would be down-weighted 50%.

PREVAIL demonstrated that the WATCHMAN device implantation could be reasonably safe with an acceptable operator learning curve.

In the PREVAIL Bayesian analysis of the updated June 2014 dataset, the WATCHMAN device failed to meet the non-inferiority endpoint compared to warfarin for the composite of all stroke, systemic embolism, and cardiovascular or unexplained death, and it failed to

meet the non-inferiority endpoint compared to warfarin for ischemic stroke and systemic embolism occurring after 7 days post-implantation.

The reason we are here is because of the additional events, which will continue to be followed for the PREVAIL trial as well as the CAP2 registry.

In determining whether the WATCHMAN device is an acceptable alternative to warfarin in evaluating whether the totality of the data support a reasonable assurance of safety and effectiveness, the Panel is being asked to address the following questions that are critical to the benefit-risk assessment of the WATCHMAN device:

- Does the WATCHMAN provide adequate protection from ischemic stroke and systemic embolism in patients with non-valvular AF?
- Is the avoidance of long-term warfarin followed by successful implantation of the device associated with a reduced risk of hemorrhagic stroke?
- Is there a clinically important signal of reduced bleeding complications due to the avoidance of long-term use of anticoagulation therapy in patients treated with the WATCHMAN device?

That completes my remarks, and I'd like to turn the podium over to Dr. Buzoianu to present FDA's statistical review.

DR. BUZOIANU: Thank you, Dr. Farb.

Good morning. My name is Manuela Buzoianu. I am the statistician on the review team. This is the outline of my presentation. First, I'll give a short introduction to Bayesian statistics. Then I'll discuss the findings from the updated PREVAIL Bayesian analysis, in particular, the incorporation of the informative prior as well as the divergence between

PROTECT and PREVAIL alone.

Bayesian methodology was adopted in designing the PREVAIL study. It is a framework for learning from evidence as it accumulates. It includes three components: the prior, the likelihood of new data, and the posterior distribution on the quantity of interest. A model is specified on which the likelihood function for the new data is based.

After the study is done, the prior distribution will be updated by the new data to obtain posterior distribution of the quantity of interest, such as the primary endpoints in the PREVAIL study. The posterior distribution is then used to perform Bayesian inference to summarize the information about the quantity of interest, particularly by point and interval estimates. In the Bayesian framework, when additional data is acquired, the posterior distributions are updated. Also, Bayesian inference is used to summarize the updated posterior distributions using point and interval estimates.

The pre-specified primary analysis for the first two primary endpoints in the PREVAIL trial involves Bayesian modeling. PROTECT AF trial data was used to provide prior information. It was down-weighted by 50% to arrive at the informative prior. In addition, a piecewise exponential model is assumed with event rates constant on four different time intervals: 0 to 7 days, 8 to 60 days, 61 to 182 days, and 183+ days.

An informative prior is specific and gives preferences to certain values of the quantity of interest. In the PREVAIL study, historical data from PROTECT AF was incorporated as prior information, such that the new trial borrowed strength from the prior study. The prior data were down-weighted 50%, resulting in 618.8 patient-years. When choosing the prior, we want to avoid having an informative prior that overwhelms the data

from the new trial: PREVAIL. Such prior may affect too much the study results and conclusions. In particular, the prior probability of study claim should be less than 97.5%, the success criterion for the posterior probability. This means that they do not consider that the study success was already met before starting the new study.

This is a graphical illustration of the informative prior distribution for the PREVAIL first primary endpoint, the 18-month rate ratio. This prior is center of the value lower than 1, in favor of non-inferiority. Also, the prior probability of non-inferiority is 97.1%, slightly lower than the success criteria of 97.5%. This probability is the area under the curve to the left of the non-inferiority boundary of 1.75.

For the second primary endpoint, the prior is centered around zero, in favor of non-inferiority. The prior probability of non-inferiority is 95.7%, slightly lower than the success criteria of 97.5%. This probability is the area under the curve to the left of the non-inferiority boundary of 0.0275.

The current study, PREVAIL, includes 407 randomized subjects with 2:1 randomization; 269 subjects were randomized to the WATCHMAN group and 138 subjects were randomized to the control group. The dataset presented to the Panel in December 2013 was from January 2013. At that time only 28% of subjects reached 18-month follow-up. The most up-to-date data available from June 2014 includes additional follow-up. In particular, all subjects reached 18-month visit. Also, the mean follow-up is 25.9 months.

According to the pre-specified analysis, PREVAIL borrows 50% of the available prior information from PROTECT AF, including a total of 618.8 patient-years. At the Panel in December 2013, PREVAIL data alone included 396.2 patient-years based on the data from

January 2013. At that time FDA noted that this amount of data was limited and the PROTECT AF prior dominated the data from PREVAIL alone. The additional data from June 2014 provides substantially more follow-up information from the new study, in particular, 860.3 patient-years in total.

This is a graphical illustration of the informative prior and data from the PREVAIL study that was presented at the Panel last year. In particular, the curves depict the distribution for the PREVAIL second primary endpoint, the 18-month rate difference. The red curve represents the rate difference prior distribution. The blue curve is the rate difference distribution based on PREVAIL only. At that time FDA noted that PREVAIL data alone appeared to diverge from the PROTECT AF prior. The prior probability of non-inferiority was 95.7%, and the probability based on PREVAIL only was 73.6%. Also, the prior appeared to be over-influential.

The additional data submitted in June 2014 provides a substantial amount of new PREVAIL follow-up, such that the prior data from PROTECT AF no longer dominate over the PREVAIL data only. The blue curve, the distribution based on PREVAIL only, is significantly distant from the red curve, the PROTECT AF prior, moving to the right in the direction favorable to the control group. Moreover, the updated probability of non-inferiority for PREVAIL only decreased to 48.8%, being substantially lower than the prior probability of 95.7%. Thus, the updated data shows an increasing divergence between PREVAIL only and the PROTECT AF.

In the next slides I'll give the update on the PREVAIL first and second primary endpoint results based on the pre-specified Bayesian approach. Recall that a pre-specified

non-inferiority criterion for the first primary endpoint is that the upper bound of the equitailed 95% credible interval for the 18-month rate ratio is less than 1.75. This is equivalent to the posterior probability of non-inferiority, for a rate ratio less than 1.75 is at least 97.5%. The criteria was not met for the upper bound of 2.05. Also, the posterior probability of non-inferiority is 92.6%.

The forest plot on the slide presents the Bayesian estimates for the 18-month rate ratio of the first primary endpoint. The red horizontal line is the 95% credible interval around the Bayesian estimate of 0.88 rate ratio based on PROTECT AF prior only, down-weighted 50%. The prior probability of non-inferiority is 97.1%. The blue horizontal line is the 95% credible interval around the Bayesian estimate of 1.84 rate ratio based on PREVAIL only. The rate ratio estimate from PREVAIL only moved considerably to the right, and the probability of non-inferiority decreased to 54.4%, raising the question of whether the device is inferior to the control group.

Using the same Bayesian approach, I performed a superiority test for the control versus device group to understand the magnitude of the divergence of PREVAIL only in the direction favorable to the control group. The superiority test compares the 18-month rate ratio to 1, which is the vertical line on the forest plot. So the probability of superiority is 91.1% for the first primary endpoint in PREVAIL only. The green horizontal line is the 95% credible interval around the Bayesian estimate of 1.21 rate ratio based on the pre-specified approach combining PREVAIL data with the prior down-weighted 50%. The additional PREVAIL data to the PROTECT AF prior appears to move the estimates to the right in a direction favorable to the control group. Also, the posterior probability of non-inferiority is

92.6%.

The non-inferiority criteria for the second primary endpoint rate difference is that the upper bound of the 95% credible interval for the 18-month rate difference is less than 0.0275. This is equivalent to posterior probability of non-inferiority is at least 97.5%. The criterion was not met for the upper bound of 0.0342. Also, the posterior probability of non-inferiority is 89.5%.

The forest plot on this slide represents the Bayesian estimates for the 18-month rate difference of the second primary endpoint. The red line is the 95% credible interval around the Bayesian estimate of 0.0003 rate difference based on the PROTECT AF prior only. The blue horizontal line is the 95% credible interval around the Bayesian estimate of 0.0284 rate difference based on PREVAIL only. The rate ratio estimate based on PREVAIL only moved slightly to the right and the probability -- moved significantly to the right and the probability of non-inferiority decreased to 48.8%. The green horizontal line is the 95% credible interval around the Bayesian estimate of 1.0163 rate difference based on the pre-specified approach combining PREVAIL data with the PROTECT AF prior.

So the addition of the PREVAIL to the prior appears to move the estimates to the right in favor of the control group. Also, the posterior probability of non-inferiority decreased from the prior probability of 95.7% to 89.5% -- the probability of non-inferiority based on PREVAIL only is 48.8%, raising again the question of whether the device is inferior to the control group.

Using the same Bayesian approach, I performed a superiority test for the control versus device group to understand the magnitude of the divergence of PREVAIL only. The

superiority test for the second primary endpoint compares the 18-month rate difference to zero, the vertical line on the forest plot. More specifically, the probability of superiority based on the Bayesian analysis combining PREVAIL data with the prior is 96.2%. Also, the probability of superiority of control versus device based on PREVAIL only is 99.7%.

The pre-specified analysis in the PREVAIL study uses a Bayesian approach, incorporating a substantial amount of favorable prior information from a portion of PROTECT AF data. In PREVAIL alone, all subjects were followed up for at least 18 months so that the current data completes the analysis of the 18-month rate. Even with a favorable prior, the first and second primary endpoints were not met based on the current PREVAIL study. Moreover, the updated data shows significant divergence between PREVAIL results compared to the PROTECT AF prior.

I'll now transition to Dr. Rachael Neubrander.

DR. NEUBRANDER: Thanks, Manuela.

As I mentioned at the beginning of this presentation, the new ischemic strokes in PREVAIL raised concerns regarding the effectiveness of the WATCHMAN device. As discussed by Dr. Buzoianu, the results of PROTECT and PREVAIL are diverging, which is problematic because the discordant outcomes of PROTECT and PREVAIL make the evaluation of the totality of the data more challenging. Based on the June 2014 data lock, the WATCHMAN device failed to meet the first and second primary endpoints in PREVAIL.

Aside from the PREVAIL endpoint results, if we look more closely at the benefit-risk considerations for this device, the rate of ischemic stroke and systemic embolism favor the control group in PROTECT AF, PREVAIL only, and the PREVAIL Bayesian analysis. Compared

to contemporary anticoagulation trials, the PREVAIL-only control group event rate was low. But when the PREVAIL-only data were combined with the discounted PROTECT AF data in the Bayesian analysis, the control group event rate was more similar to other anticoagulation trials with overlapping confidence intervals.

There was a signal of reduced hemorrhagic stroke with the WATCHMAN device in PROTECT AF. However, the event rate in the PROTECT AF control group was high compared to other anticoagulation trials. In addition, upon review of the individual events, the robustness of this benefit signal was also tempered by the circumstances surrounding these events, including non-use of warfarin in one subject, no CNS imaging in another subject, concomitant use of antiplatelet agents, and potential adjudication challenges when cranial bleeds were associated with head trauma.

In terms of cardiovascular or unexplained death, the benefit of the WATCHMAN device in PROTECT AF was driven by a reduction in fatal hemorrhagic strokes, which is important to keep in mind given the considerations Dr. Farb discussed regarding the hemorrhagic stroke data. Aside from hemorrhagic strokes, cardiovascular or unexplained death event rates did favor WATCHMAN, but the events were unlikely to be related to the device or to warfarin.

Finally, there was a signal of reduced late bleeding in WATCHMAN subjects compared to control subjects. However, there was no difference in overall bleeding rates in PROTECT AF or PREVAIL.

This concludes the FDA presentation. I'd like to thank the entire Panel for their time and attention.

DR. PAGE: Thank you very much. I'd like to thank the FDA speakers for very clear presentations.

I will comment. There will be a challenge because we have handouts with slide numbers that differ from the slide numbers that were projected. So that will be a bit of a challenge for us. And, ideally, what we see on the screen is what we have in hand.

I'll now ask panelists whether they have any clarifying questions.

Dr. Cigarroa and then Dr. Kelly.

DR. CIGARROA: I'd like to know whether or not the FDA looked at any subgroup analysis with regards to gender. It's well known that ischemic rates in female gender, individuals who have atrial fibrillation, are higher than males. So was that looked at or discussed at any point?

And the second question is along the probabilities of hemorrhagic complications. Did FDA look at estimated GFRs, and that is, patients on antithrombotic and/or antiplatelet therapy who have renal insufficiency are at much higher rates of hemorrhagic complications?

DR. FARB: So thank you. Regarding the gender, I believe we did look at that, and we'll confirm that during the break, and I would also confirm it with the Sponsor, that there was no identified subgroup differences for which the device would have been more or less beneficial versus control.

With respect to GFR estimates, GFR based on creatinine, I don't think that evaluation was done. It's an important question.

DR. CIGARROA: Thank you.

DR. PAGE: Thank you.

Dr. Kelly.

DR. KELLY: I have two questions for Dr. Farb. The first is -- and it refers to Slides 84, '5, and '6, although we don't absolutely have to see them. Do we have ejection fraction data on these people? I mean, the control group had more MIs and more ICDs and heart failure was similar, but again, we don't know which of those people had heart failure with preserved ejection fraction, which carries a lower risk of sudden death. Do we know ejection fractions on the two groups?

DR. FARB: Those data at baseline were available because part of the initial evaluation included echocardiography and there was an estimate of ejection fraction, but I don't know if there was an analysis, a subgroup analysis based on the two with respect to mode of death.

DR. KELLY: Were they comparable ejection fractions between the two groups? They're not in the --

DR. FARB: I believe they were. Again, we can double-check that and also check with the Sponsor.

DR. KELLY: Okay. And the second question is -- you know, we've been encouraged to look at the totality of the data. And that's fine, but it's also a little confounded by the fact that the two groups aren't exactly the same. The PREVAIL people, by design, are higher risk and they have more MIs, they've had more prior strokes, which are both heavily weighted risk factors. So when we originally in 2009 looked at the PROTECT data, I believe we had 900 patient-years, and now PREVAIL, we have 860. So although the original

PREVAIL data from 2013 weren't powered to look at efficacy, I'm wondering if now they are.

DR. FARB: When you say efficacy, are you talking about the composite of all strokes that includes --

DR. KELLY: Well, all strokes. Yeah.

DR. FARB: Yeah, I think that those analyses were completed with the updated greater than 2,100 patient-year dataset of PROTECT.

DR. KELLY: Right. But when we looked at the PREVAIL data in 2013, we were heavily weighted towards looking at safety because the data were too small to really look at efficacy.

DR. FARB: Um-hum.

DR. KELLY: But now that we have 860 patient-years, is it powered? Could we look at that study alone and say it's powered for efficacy?

DR. FARB: Well, I think Dr. Buzoianu has shown some of those data showing that indeed there is -- with that amount of follow-up, we can draw some conclusions about that dataset with respect to the -- particularly with respect to ischemic stroke.

DR. KELLY: Okay, thank you.

DR. BUZOIANU: I would like to add that PREVAIL was powered for the combination of 50% discounted PROTECT AF with a limited follow-up from PREVAIL. That data was presented at the last Panel. Now, we have -- we present PREVAIL only with additional -- with substantial additional follow-up, so a total of 860 patient-years. But the power was done for the data presented at the Panel last year.

DR. FARB: The numerical signal for ischemic stroke was present, just beginning to be

present at that first Panel meeting, of five to one.

DR. KELLY: Thank you.

DR. PAGE: Did that answer your question, Dr. Kelly? Specifically, I thought I heard you ask the statisticians whether we can look at PREVAIL alone and whether they feel that meaningful data come from that study and, in fact, whether we should look at them because, in retrospect, perhaps the PREVAIL and PROTECT populations might be different. Did I understand your question?

DR. KELLY: Yes.

DR. PAGE: And I'm not sure I heard the answer to the question.

DR. KELLY: Right, that was my question. You know, again, the PROTECT -- at the original Panel meeting we had back in 2009, there were, I believe, 900 patient-years. So we kind of looked at that as if -- you know, we looked at safety and efficacy as if we had some kind of answer from that. Then in 2013 with PREVAIL -- I think I remember -- we really considered safety because the dataset was just too small, but now it nearly equals what PROTECT did. So I'm wondering if we can give it more weight or not. And can we look at it again as a separate trial as opposed to considering the totality, given the inherent differences in the population?

DR. ZUCKERMAN: Okay. So let's take a timeout here to clarify certain things. Number one, when we say the PREVAIL study, Dr. Kelly, it was designed as a Bayesian trial, as Dr. B. has pointed out, with 50% down-weighting of the PROTECT AF plus the PREVAIL data. And that's what you saw in December 2013. And at that time we were not just presenting safety, as you've alluded to, because there was a predictive capability to the

model, such that even though 28% or so had technically only reached their 18-month follow-up, we could predict results for the whole cohort. That's what you saw. They were borderline, and be it as it may, the Panel made certain decisions.

Now, at this point, as you've pointed out, we can look at the PREVAIL-only dataset with the caveat that that was not the prospectively pre-specified analysis. The review team can get that together with the Sponsor, but you do need to look at all of these additional analyses in the vein that these are somewhat post hoc but valuable.

DR. PAGE: Thank you very much.

I will be calling on Dr. Furie and then Dr. Yuh and Dr. Cigarroa.

Dr. Furie.

DR. FURIE: Thank you.

Do you have an analysis of the intracerebral hemorrhage that subtracts out those on dual therapy, warfarin and an antiplatelet agent, and also eliminates the subdural hematomas, which, as you point out, are not technically hemorrhagic stroke?

DR. FARB: We just have the narrative summaries, so it's sometimes difficult to be able to pick and be able to go back to source documents and be able to figure it out. And sometimes the information is not available. But I think that the message overall is that these hemorrhagic strokes had other issues going on that may have particularly increased the risk of these events in these certain individuals, and that I can go back to the slide of how many of those patients were on -- I think it was about five. I'll have to go back to look and acknowledging that it can be difficult sometimes to adjudicate some of these events. Did the fall occur because of the hemorrhagic stroke or did the patient fall on the ice and

down the steps? But the idea is that these are all significant bleeding events that can be fatal and that you need to just not consider hemorrhagic strokes. You should also consider these cranial bleeding events.

DR. FURIE: And did I hear you correctly that subdural hematoma counted as a hemorrhagic stroke for the controls but not for the WATCHMAN?

DR. FARB: Well, again, there were at least three cases of patients in the WATCHMAN group who had fallen and had subdural hematoma but were not adjudicated as hemorrhagic stroke. We asked about that. In the best judgment of the CEC, that's how they adjudicated it. But, again, it can be -- compared to some of the other narrative summaries, which on their face appear to be somewhat similar -- fall and hit your head on the ice and have a subdural hematoma adjudicated as hemorrhagic stroke -- it can create some difficulty there.

DR. PAGE: Thank you.

Dr. Yuh.

DR. YUH: Thank you. You know, a lot of FDA's concerns seem to be focused on the failure of the device to make non-inferiority thresholds. Take me through, you know, not being a statistician, as a surgeon, and so you have to talk really slowly. Explain to me how the posterior probability for non-inferiority is derived and the real-world rationale behind that, because a lot has hinged on that, on not making that threshold, and I just want to understand how that threshold was derived and how it's relevant to this particular comparison.

DR. BUZOIANU: I think, about the threshold, Dr. Farb might have a better comment.

That was pre-specified in the initial analysis plan for PREVAIL. As I previously said, the pre-specified analysis included 50% discounted PROTECT AF data and PREVAIL only with 28% of patients completed follow-up at 18 months. That was the pre-specified plan. Now, we are looking at substantially more -- we are adding substantially more follow-up in the PREVAIL trial, and we are looking at the pre-specified analysis combining 50% PROTECT AF with substantially more data from PREVAIL only. The combined approach gives us posterior probability.

DR. YUH: I guess I'm just not understanding the connection between a 97.5% posterior probability threshold. I mean in theory, you know, the non-inferiority is to show that this device is not worse than Coumadin therapy. So my rudimentary understanding of a non-inferiority test is that the thresholds are often based on historical controls, for example, Coumadin versus placebo or Coumadin versus no therapy. So I'm just trying to -- I know you're into the pre-specified criteria, but that doesn't help me understand it.

DR. PAGE: Dr. Zuckerman, help us out here.

DR. ZUCKERMAN: Okay. So, Dr. Yuh, would you like Dr. Buzoianu to go back to the slide where she had the three horizontal lines for the second primary effectiveness endpoint and just walk you through that?

DR. YUH: That might be helpful.

DR. PAGE: And after we do that, Dr. Zuckerman, I might ask for -- while the FDA group is doing a great job of explaining as best they can to the Panel, and we are not statisticians, maybe if you can enlighten the Panel a little bit further on the concept of the Bayesian analysis. In review of the last Panel, I'm not sure everybody gets it and I'm not

sure I completely get it. So, if you can, as a cardiologist/non-statistician but an expert in this area, help bring what is, I'm sure, being explained adequately to the Panel so that the Panel can really understand the concept behind the Bayesian analysis.

DR. ZUCKERMAN: Okay. But, Manuela, could you show -- do you have the similar type slide for the second primary endpoint or just for this one? Perfect. Hold it there.

Okay. So the first thing is to understand where FDA was at the conclusion of the first Panel meeting in 2009. We had the PROTECT AF trial, but a very informative Panel discussion indicated that there were problems with the design and execution of the PROTECT AF trial. Hence, even though there appeared to be a signal with an appropriate p-value, the real meaning of the signal and the p-value was still questionable as to what it represented. However, we didn't want to throw the baby out with the bath water because a well-done randomized trial with some merit was there, and consequently we chose to build upon the PROTECT AF dataset.

Now, in building upon the PROTECT AF dataset, as Dr. Buzoianu has pointed out, we down-weighted using a standard technique, the merit or signal intensity of the prior. And that's shown by the top horizontal line, the PROTECT AF prior, and you see what the mean is and the 95% credible interval. In the Bayesian terminology, you then build upon that prior by accumulating new data, and that's where the PREVAIL trial comes in, and the PREVAIL-only data with the point estimate and 95% confidence interval or credible interval is shown on the third line.

Now, to everyone's surprise, you can see that the mean value, as well as most of the credible interval, is to the right of the so-called non-inferiority line that Dr. Yuh rightly

points us to. And, hence, even though when we combine the two datasets in the middle green horizontal line, the median value is certainly on the correct side. You'll see that there's not as much weight now to non-inferiority, as noted by the value of 80-something percent. But just as importantly, it's important to look at the data, as Dr. Buzoianu was instructing us, just to look at where the medians are and to notice how divergent these two curves are that we're trying to combine for an overall final posterior probability.

Manuela, can you continue?

DR. BUZOIANU: I would like to add that the probability is the measure of uncertainty. When the data, the PROTECT AF prior data, was favorable to the WATCHMAN device, when the data was down-weighted by 50%, that means that we have -- at that time we discounted the variability in that data, not necessarily the effect of the result in PROTECT AF. So the discount of 50% means discounting variability and means less uncertainty about the effect of the device. So the success criterion of 97.5% for the prior only down-weighted 50% -- and we have 95.7%, so less than the success criterion. That means that we wanted to have less uncertainty about the favorable effect, but it was still a favorable prior. The point estimate is 0.0003.

And while the Bayesian approach is adding data from PREVAIL to the prior and we can see -- adding the data and then looking at the data alone without the prior, we can see the divergence, you can see the estimates moving to the right and showing -- the right side of the graph represents inferiority of the device versus control, and also the point estimate based on the combined approach is 0.0163 and based on PREVAIL data only without the prior is 0.0284.

DR. PAGE: Thank you very much.

Dr. Yuh, is that answering your question? I thought you were -- part of your question was why the 50% discount as opposed to 25% or 100% discount, and likewise the setting of the non-inferiority boundary. Was that what you were driving at for clarification, that number?

DR. YUH: Yes, exactly. From a practical standpoint, how do you arrive at deciding the 50% downgrade of the weight and then the calculation of the 97.5% posterior probability?

DR. FARB: So I can start to address the 50% weight. I think, as you recall, the PROTECT AF data with 900 patient-years was not adequate to support approval of the device. And that was an agreement based on the limitations of PROTECT that we've outlined, to use some of that PROTECT data and use a reasonable amount of it so that, as Dr. Buzoianu said, it wouldn't overwhelm the new important data that could be generated to help support device effectiveness.

So it was a consensus decision between the company and FDA if that was a reasonable amount, keeping in mind that we wanted a trial that could be done with a feasible number of patients to get to the message that the device is safe and effective or is not, and then within that framework, to also craft clinically reasonable non-inferiority margins, again with those other parameters in mind, to have a trial that could be feasibly done and show that if the device met non-inferiority, that would be clinically acceptable for physician use for patient benefit.

DR. PAGE: Thank you.

I have on deck Dr. Cigarroa, Dr. Kandzari, and Mr. Thuramalla, but I've been looking to Dr. Naftel to weigh in, and now he will enlighten us, I hope.

DR. NAFTEL: Perhaps. This is really an exciting discussion. Is there anybody that's not excited?

(Laughter.)

DR. NAFTEL: So just a couple things. The whole basis of Bayesian analysis is to build on experience. And that's been said very adequately. So, you know, if you followed the exact rules, you would have all your old data, you'd add new data to it, and you'd have a new analysis. But then you have to be pragmatic, and the 50% is you are backing away from a true Bayesian analysis because you're nervous and you clearly stated that you didn't want the earlier trial to overwhelm the new one, which that's code for saying the new one doesn't have a large sample size compared to the original one. So you're a little nervous and don't want the old to overwhelm. Then we're stuck in this incredible position where, once you do the Bayesian analysis, you're still nervous because your new trial, the PREVAIL, has apparently different results.

So we're really teetering back and forth between Bayesian and non-Bayesian. And I don't blame us. I think we should we do that. But if we were pure Bayesians, we'd never show the blue line, you'd only show the green line. But we just can't live with that. So that's why we keep going back to the absolute rates and we keep discussing the trial data as it is. So it's interesting. It's a divergence from pure Bayesian analysis, but I personally think it's absolutely appropriate, just what you're doing and how you're presenting it.

DR. PAGE: Thank you very much.

Dr. Cigarroa.

DR. CIGARROA: So I'm going to expose some of my statistical shortcomings. In non-inferiority trials, I'm used to thinking about comparing Drug A versus Drug B. You know, we look at bival versus heparin in the interventional world, and one looks and says, maybe they're within about 25%, and I'm willing to accept that and that's in the statistical methodology. Where I'm having trouble is not on the concept of the analysis but the concept of how do I equate that with posterior probability and where that margin is? I'm just not seeing that and therefore finding it difficult to translate into the world that I know.

DR. FARB: Well, I can start. I mean, I think the same kind of thinking goes into both thinking about posterior probability and frequentist type of approaches in terms of uncertainty and the probability of inappropriately conducting null hypotheses. But I hope the statisticians will probably answer it much more eloquently.

DR. BUZOIANU: I can probably go over the criterion that we have. So the criterion is that the upper bound of the 95% credible interval is less than 0.0275. This is the same thing as saying that the posterior probability of non-inferiority -- that the rate difference is less than 0.0275 is the same thing as saying that this posterior probability is at least 97.5%. It's just a mathematical calculation, and these are two equivalent criteria.

DR. PAGE: Does that clarify things for you, Dr. Cigarroa? We're all working through this, and we will have more time after lunch as well.

(Off microphone response.)

DR. PAGE: Thank you.

Dr. Kandzari.

DR. KANDZARI: Thank you. This is a question for Dr. Farb. Andy, you began the introduction by stating that the real test in some ways would be a comparison of the device with aspirin therapy relative to warfarin anticoagulation, and I wanted to amplify that because we've focused our discussions on prior datasets to December '13 to present. But I have not been able to find, in any of the documents, any analyses that might be analogous to a landmark analysis of looking at the events of both bleeding and intracranial hemorrhage and ischemic stroke from, say, 6 months, the time of pure aspirin therapy alone, to present data in both groups.

DR. FARB: So, at least in respect to the PREVAIL-only dataset, those ischemic strokes, of the 13, they're all -- 12 of the 13 occurred with the patients beyond the 6 months. So the vast majority of those were on that destination therapy that you alluded to. In the PROTECT data, recall from the prior Panel that once we got further out with PROTECT, that there was enough further divergence of curves of ischemic stroke and systemic embolism between PROTECT and PREVAIL, giving some reassurance back then that longer term -- you know, that the device was holding up pretty well. So, again, it does feed back to where you have two trials that have somewhat heterogeneous results and that give different messages.

DR. KANDZARI: Can you just clarify for me, then? You mentioned ischemic stroke on destination therapy. What about hemorrhagic events, were those --

DR. FARB: Well, the hemorrhagic events in PREVAIL were -- there were only two in each group, so it's really kind of hard to know much about those.

DR. KANDZARI: Thank you.

DR. PAGE: Mr. Thuramalla, did you have a comment, a question?

MR. THURAMALLA: Firstly, thank you for an excellent presentation to Dr. Farb and all the FDA members.

I have actually four comments, and I'll start with the first one. On Slide Number 85 -- and the numbers I am referring to are the ones that you showed us. So on Slide Number 85, my question is, is there a p-value to indicate whether it is statistically significant or not? Slide Number 85.

DR. FARB: Could you give us the title of the slide, I guess, just to make sure?

MR. THURAMALLA: The title of the slide is "Hemorrhagic Stroke and Cranial Bleeds." It's comparing the WATCHMAN group with the control group.

DR. FARB: I think we have that up. And no, we did not calculate a p-value for that.

MR. THURAMALLA: On Slide Number 99, I just wanted to clarify on the total number of the first column. It says 50. The title of the slide is called "PROTECT AF Major Bleeding." And I think, sorry, the slide number is 97. "PROTECT AF Major Bleeding."

DR. FARB: This is a similar slide. It just had some color.

MR. THURAMALLA: That is correct. So the total major bleeding on the first column says 50. So I couldn't really find out how it's 50. I was trying to add 28 plus 24, so I'm thinking there must be some redundancy there or --

DR. FARB: Could you direct me to where --

MR. THURAMALLA: The very first column, 50 or 463. I'm trying to understand how did we arrive at the number 50, because if I add the procedure related and the non-procedure related, that's going to be 52.

DR. FARB: Okay. Yeah, we'll have to go back and check that. This was an analysis that the Sponsor performed for us, so we'll both have to put our heads together.

DR. PAGE: Might it be possible that two patients had both procedural and post-procedural bleeding to account for --

DR. FARB: That's a possibility as well. Yeah, this is probably not hierarchical, and that's probably a good point.

MR. THURAMALLA: So the next one I had was on Slide Number 82 and this -- maybe to the Chair, I would like to request maybe both the FDA and the Sponsor to help us understand. On Slide Number 82, the way I have commonly seen as a standard practice is it's the intent to treat that is what is used while analyzing randomized clinical trials. So, to come to the conclusion, I want both the Sponsor and the FDA to help me understand that.

DR. PAGE: Just take a look at the screen and make sure we're looking at the slide you're talking about.

MR. THURAMALLA: That is the correct one.

DR. PAGE: Great, thank you.

MR. THURAMALLA: I'll wait for the Sponsor to have one last comment.

DR. FARB: So you're exactly right. And I did make the comment that this patient was appropriately considered in the intention-to-treat sense for the control group. However, to get a little bit more insights into the risk of hemorrhagic strokes and the number of hemorrhagic strokes, this was important information.

DR. PAGE: Dr. Stein, right now -- we'll bring you up if that's appropriate at this time. Right now we're asking questions of FDA.

DR. STEIN: Well, we're in agreement.

MR. THURAMALLA: And then the last one, Slide 85 -- sorry, Slide 84. The three WATCHMAN subjects fell, presenting in subdural hematoma. I also wanted to the Chair to request the Sponsor to shed some light on that, as to why did they include or not include those patients in their analysis.

DR. PAGE: Okay. And questions to the Sponsor we'll be holding off until after lunch, unless there's a specific analysis that we're thinking needs to be addressed. Otherwise we will have plenty of time to involve the Sponsor as well as the FDA in discussion.

MR. THURAMALLA: Sure. My only reason for bringing it now is if there needs to be an analysis done, then this may be a time so it would give the Sponsor enough time to look into it.

DR. PAGE: Okay, why don't you go ahead and restate the question.

And, Dr. Stein, do you want to comment?

MR. THURAMALLA: I'll restate my question. I just want to understand. On the three WATCHMAN subjects that fell, presenting in subdural hematoma, were these cases not adjudicated as hemorrhagic stroke? If that is the case --

DR. STEIN: I can address -- and I don't know if you wanted me to address the other question. I'll start just with that because I think it also gets to those p-values that you asked for. So I think it's important if I just first bring up the pre-specified consistent adjudications that were used by the CEC in determining what was a hemorrhagic stroke. And this was pre-specified in the protocol. And so in PROTECT AF, a hemorrhagic stroke required the sudden onset of a focal neurologic deficit with imaging evidence of tissue loss and evidence

of hemorrhage intraparanchymally. So a traumatic hemorrhage that was limited to the subdural compartment was defined as a cranial bleed and was not defined as a stroke.

PREVAIL was slightly different, so that in PREVAIL, any focally symptomatic intracranial hemorrhage was adjudicated as a hemorrhagic stroke. So that did allow for a subdural hematoma to be adjudicated as a hemorrhagic stroke in PREVAIL. If we actually look at what the adjudication was, there was only one subdural hematoma adjudicated that way in PREVAIL, and it was in a WATCHMAN patient, so really to the disadvantage of the device. But, again, that's the pre-specified definition, and that's what we went with for our calculations.

The three PROTECT AF warfarin group patients who had subdural hematoma adjudicated as hemorrhagic stroke, in all three there was also evidence of intraparenchymal bleeding. And I think, as we mentioned, you get into that adjudication difficulty. You know, was this a primary hemorrhagic stroke with a secondary fall and subdural hematoma or vice versa? So I'd like to go now to the slide where we actually look at the cranial bleeds versus the subdural hematomas.

DR. PAGE: I'll tell you what. This is a very important topic for discussion. We only have 15 more minutes, so I'm just going to take a time check in terms of panelists' questions for the FDA, because this is our time to ask the FDA questions before the lunch break.

(No response.)

DR. PAGE: I'm not seeing any burning questions from the Panel, so go ahead and proceed. Thanks.

DR. STEIN: So let me come up -- so this is really the slide that the FDA showed, but we've added in the p-values, I think, as someone had requested, for the distribution of hemorrhagic strokes and then the adjudicated cranial bleeds and then the total. And so within PROTECT AF -- again, to begin with, I think it's critical to remind everyone of the 2:1 randomization.

So these are raw numbers, but adjust them in your heads, that there are twice as many WATCHMAN subjects as warfarin subjects. As you've seen, the CEC-adjudicated hemorrhagic stroke rate is markedly different between the two groups, with a p-value of 0.002. For adjudication of non-hemorrhagic stroke/intracranial bleeding, the difference between the two groups is non-significant. It's a p-value of 0.439, indicating that that distribution is very likely to have occurred on the basis of chance and that it does not reflect any inconsistency in adjudication by our CEC.

But, finally, we've done a sensitivity analysis and said, all right, let's include every one of those cranial bleeds, the pure subdural hematomas, and count them as hemorrhagic strokes. In that case, still, it's a 1.7% rate in WATCHMAN versus a 4.5% rate on warfarin. And even with that very conservative sensitivity analysis, the difference in hemorrhagic strokes between WATCHMAN and warfarin in PROTECT AF remained statistically significant.

DR. PAGE: Thank you very much.

Looking to the Panel for further questions for the FDA.

(No response.)

DR. PAGE: Wow. We are at 10 minutes of, so we will actually -- we will be starting again at 1:00 with the open public comment section. I'd like to thank the FDA speakers for

their presentations. And we now will be breaking for lunch.

Panel members, please do not discuss the meeting topic during lunch with anyone. We'll reconvene exactly at 1:00. Please take your personal belongings with you. The room will be secured by FDA staff during the lunch break. You'll not be allowed back into the room until we reconvene.

I will also mention for any of our public comment speakers, we're going to have 4 minutes and people are going to be cut off at exactly 4 minutes. We'd love to have 3-minute presentations. We'll be starting promptly at 1:00.

Thank you.

(Whereupon, at 11:49 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. PAGE: I would like to resume this Panel meeting. We will now proceed to the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Waterhouse will now read the Open Public hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PAGE: Thank you very much.

Today we have 14 requests to speak. This number is unprecedented in my

experience, and we have an hour to go through these presentations. As such, we will not be inviting any unannounced public speakers during the hour we have allotted. I'll ask that everyone speak clearly into the microphone, and for anybody with mobility issues, you're welcome to sit at the table if you would prefer that over standing at the lectern. And we'll ask you to clearly state your name and respond, as Ms. Waterhouse just mentioned, in terms of any conflict you might have, but that will not preclude you from speaking.

The other thing I'll mention is we only have 4 minutes per person. The yellow light will go on at 3 minutes, and there will be a beeper and the red light goes on at 4 minutes. I'm going to be very strict about the timing, and the reason is I know you all have important things to say, so I can't allow an earlier person to take a minute away from the next deserving speaker. So we will be very rigorous about staying on 4 minutes, and I really ask the speakers to help us out with that.

The first speaker is -- and I apologize if I mispronounce the name -- Saibal Kar from Cedars-Sinai Medical Center.

DR. KAR: Thank you, everybody. May I introduce myself? My name is Dr. Saibal Kar. Nice, you pronounced it. I'm the Director of Interventional Cardiac Research in Cedars-Sinai Medical Center, Los Angeles. I'm one of the lead enrollers of the CAP and the PREVAIL trial, and I also serve as the national co-PI with Dr. Doshi for the CAP2 registry, and I serve as an international proctor.

Although Cedars-Sinai has been largely known as a celebrity hospital or a boutique hospital, we are actually a community and an academic center and have been involved in all the three large structural heart disease trials. I'm here in this limited time to speak on

behalf of the select group of patients who have waited and suffered for over a decade for this technology that might be useful to them.

Most of these patients that we dealt with in these trials were patients who, for various reasons and difficulties in taking Coumadin or NOACs, were actually referred to us. In fact, this is particularly true in the registries, where we could see the patients could not even take long-term medications. While consenting and admitting these patients as candidates to the studies, the short-term risks of the procedure, the long-term risks of the procedure, and the potential benefits and risks were explained to them.

During the last years, 8 years in Cedars, we have treated over 100 patients with the WATCHMAN device. With 100% deployment success rate, there have been only two patients with pericardial tamponade treated percutaneously, no cases of device embolization, and no cases of periprocedural stroke. On follow-up, while we discuss with these patients, we would tell them that this does not eliminate the risk of stroke. This reduces the risk of stroke and only reduces stroke from an embolism from the left atrial appendage, and you can still have another cause of a stroke.

Over this period of 8 years we've actually had three patients who sustained neurological events, and I want to talk about those three events. There's one patient, as you had described, Dr. Noonan, a person who had a thalamic stroke who came to me 18 months after the procedure and that did very well. It was a small thalamic event and was actually potentially not considered to be related to LA appendage, and a TEE showed no thrombus on the device. The two other events that took place were people who had subtle neurological deficits 6 months prior. When they came for follow-up, there was

actually no deficit. The imagings done at the time of event and what we did showed no event. The CEC, which is apparently better than us, actually adjudicated them as ischemic events. There's not a single patient who has had a disabling ischemic event in the last 8 years.

We've had, on the other hand, some bleeding events, and one of them, as mentioned today, is a patient who had a subdural hematoma 10 days after his WATCHMAN procedure. He actually fell down, hit himself in the bathroom, hit his head, and was admitted into the hospital. Most people do agree that hitting your head on the bathroom tub has nothing to do with the WATCHMAN device. The patient subsequently succumbed to the subdural hematoma over the next few weeks and died.

In addition to this data that has been presented, I do want to mention a few words about the CAP registry, which we clearly show is more of the real-time data, and you can see that most of these patients did extremely well with a high procedure success rate.

Finally, at the present moment, I would like to say that in the United States -- there is no endovascular LAA occlusion device available in the U.S. at the present moment. This makes it very frustrating for both patients as well as referring physicians. We present today a truly transforming technology that will not necessarily -- I agree, not necessarily be the first-line treatment but rather a therapeutic option for those who cannot or those who should not be taking long-term anticoagulation, for example, as Dr. Furie mentioned, people who have had stents and are on dual antiplatelet therapy. In fact, these would not have been included in the study. We hope that your --

DR. PAGE: Thank you very much.

DR. KAR: Thank you very much.

DR. PAGE: The next speaker is Daniel Lustgarten, Dr. Daniel Lustgarten, from Fletcher Allen Health Care, University of Vermont.

Welcome.

DR. LUSTGARTEN: Thank you very much. As mentioned, my name is Dr. Daniel Lustgarten. I am an electrophysiologist at The University of Vermont Medical Center and Associate Professor of Medicine at The University of Vermont School of Medicine in Burlington, Vermont. Boston Scientific has paid for my travel here today but not my time, and I have no financial interest in the company or the WATCHMAN device.

I was principal investigator at my center for both PREVAIL and CAP2. I was invited to participate in PREVAIL as a new center with no prior WATCHMAN experience, fulfilling part of that study's mandate to explore the safety of WATCHMAN implantation in the hands of operators without prior left atrial appendage closure device implant experience. In that context, I successfully implanted 19 devices out of 21 that were attempted and had only one procedural complication, which was a pericardial effusion that responded readily to pericardial draining. To date, we've had no procedural strokes, no dislodgments of the device, no strokes subsequent to device implantation.

Based on the findings of PROTECT AF, PREVAIL, and CAP registries, on my own experience implanting the device and on the responses to the treatment I have witnessed in my patients who have received it, I grow increasingly frustrated that I cannot offer my patient population this vitally important life-saving alternative to anticoagulant therapy. I treat well over 1,000 Vermonters and northern New Yorkers afflicted with this disease

process. It is critical for me to be able to offer those at highest risk the best possible options to lessen their probability of severely debilitating or lethal strokes. Many of these patients are reluctant to accept the long-term bleeding risks associated with these drugs, or can't tolerate long-term treatment due to drug intolerance and/or bleeding problems, or have referring physicians unwilling to sanction anticoagulants in their patients, sometimes with and sometimes without good reason. Currently, the alternative treatment option in these patients is to do essentially nothing, which in effect means waiting to see just how bad their first stroke is going to be.

In addition to the human cost of under-treatment, indirect and direct costs of the strokes associated with AF are estimated to be about $15 billion a year in this country. This is an era of the Coumadin gold standard. The compliance issues associated with anticoagulants have not been eroded by the relatively simpler novel agents now available. Patients' concerns regarding the dangers of anticoagulant therapy, coupled with physician reluctance to prescribe, has created a glass ceiling that devices like the WATCHMAN can help us break through, which would be to the benefit of the patients for whom we care and for our severely stressed healthcare system.

In my view, for some time now we have had sufficient evidence to support approval of the device, an opinion apparently shared by this Panel, who has voted in favor of the device twice since 2009, and last year's vote overwhelmingly so. The perspective I would ask the reconvened Panel to incorporate as you make your decision today is that of the frontline invasive EP practitioner like myself, who for the past 15 years has been struggling to prevent the worst aspect of atrial fibrillation, namely a stroke, sometimes with

heartbreaking and distressing outcomes.

The studies upon which we judge the quality of treatments are best-case scenarios in which we compare a novel treatment with current state-of-the-art treatment. In practice, with respect to AF management, the choice is more often than not an anticoagulant or no treatment at all, the latter estimated to represent 50% of the patients in this country who ideally should be treated. There's absolutely no doubt in my mind, based on my clinical experience and my experience with the device, that should the WATCHMAN device be approved, I will be treating patients in my practice who otherwise will be receiving no therapy and that lives will clearly be saved and devastating chronic illness prevented as a consequence.

Thank you very much for taking these less than 4-minute comments into account.

(Laughter.)

DR. PAGE: I do want to applaud you and thank you, Dr. Lustgarten. And I would mention that often people's final statement is what we want to hear, and I hate the idea of cutting them off. I'm not a mean person, but we will be cutting people off just because I want to be generous to the next speaker.

Speaking of the next speaker, Christina Silcox, a Senior Fellow at the National Center for Health Research, is here to address the Panel.

Welcome.

DR. SILCOX: Thank you for the opportunity to speak today. I am Dr. Christina Silcox. I have a Ph.D. in medical engineering and medical physics from MIT, and I'm a Senior Fellow at the National Center for Health Research. Our research center scrutinizes scientific and

medical data and provides objective health information to patients, providers, and policymakers. Those are the perspectives I bring with me today. We do not accept funding from device companies, and so I have no conflicts of interest.

We all know that AF patients are at high risk of ischemic stroke. Warfarin is a well-established and effective treatment, and other new therapies provide safe and effective alternatives. Any new treatment should thus show clear evidence that the benefits outweigh the risks. Like many of you, we are skeptical that the WATCHMAN device achieves that goal.

The PREVAIL study shows that the WATCHMAN device is inferior to warfarin for two of the three primary endpoints. Ischemic strokes and systemic embolisms occurred at higher rates in the WATCHMAN group compared to the control group. Most troublingly, most of the ischemic strokes occurred more than 1 year after implantation. In the PREVAIL study, twice as many patients experienced an ischemic stroke or systemic embolism in the second year after implantation than in the first. Longer-term data is clearly needed to determine if the device is losing effectiveness or if the device itself is causing these events.

While the PROTECT AF data includes 5 years of follow-up, many implanted patients also took oral therapies, confounding the results. The Sponsor's proposed postmarket study includes only 2-year endpoints and lacks a control group. That is not adequate to evaluate long-term safety or effectiveness of a permanently implanted device, and it is unclear what chronic antiplatelet drugs would be allowed in this postmarket study which could lead to the same analysis issues as the PROTECT AF study.

The major potential benefit of the WATCHMAN device is a decrease in hemorrhagic

strokes. Unfortunately, the small number of patients in the PREVAIL study and the low incidence of hemorrhagic strokes means the results were inconclusive. The problematic PROTECT AF trial did show a decrease in the incidence of hemorrhagic strokes, but the control group had more hemorrhagic strokes than other warfarin studies, so it is difficult to draw conclusions.

The PREVAIL trial showed fewer major bleeding events after 6 months post-implant, but WATCHMAN patients had major bleeding related to the surgery, which makes up for the lower bleeding rate later. So long-term data is needed to determine if this is actually a risk or a benefit. We are glad to see that additional training may reduce the rate of complications from surgery. But since clinical trials tend to include the best physicians, it would be unrealistic to think that most AF patients would find surgeons with that level of training and expertise.

In summary, patients implanted with the device are at increased risk for ischemic stroke. Methodological problems make it difficult to assess if the device reduces hemorrhagic strokes. The decrease in major bleeding events after 6 months is negated by the increased bleeding events due to surgery. The device is inferior to warfarin for two of the three primary endpoints identified by the Sponsor and the FDA as signifying success. That's why we urge you to vote no. The data do not prove that the benefits outweigh the risks or provide a reasonable assurance of safety or effectiveness.

Thank you.

DR. PAGE: Thank you, Dr. Silcox.

Our next speaker is Mauricio Sanchez, Director of the Electrophysiology Laboratory

at Mercy Heart and Vascular Hospital.

Welcome.

DR. SANCHEZ: Thank you very much. I wanted to thank the Panel for the opportunity to speak. My name is Mauricio Sanchez, and I am an electrophysiologist, and I practice in the community. I am also a member of the left atrial appendage advisory board and a proctor for Boston Scientific. I was an investigator, a site investigator, for the PREVAIL and CAP2 registries and one of the new implanters, implanting in approximately 52 patients in those two trials. And I'm here today to ask for options, options for the patients that we treat in the community and options for patients that suffer from AF.

There's no doubt that today patients have significantly more options than they had years ago. Nonetheless, you all are very familiar with the data. Patients are under-treated. Most patients never make it to my office. They're stopped at their primary's office. They're not candidates, they're told. Even with novel agents, 17% to 25% of patients cannot or will stop taking their novel oral anticoagulant.

And what happens with these patients? We see these patients every day in the clinic, we see these patients in the hospital, and I have one here with me today who's been gracious enough to make the arduous journey here, who had a GI bleed and ended up in the ICU and after having three units of packed red blood cells was eventually discharged. He's had a previous stroke, and he has to make the choice to being at risk for stroke or being at risk for bleeding. When your creatinine -- excuse me -- when your hematocrit is low, taking the plane ride here wasn't that easy, and he required oxygen, but he believes strongly in being here to have this option, to have this option for patients that otherwise are choosing

between the high risk of bleeding and the high risk of stroke. I think the data and my experience tell me that that is sufficient to give some of these patients this option.

Thank you very much.

DR. PAGE: Thank you, Dr. Sanchez.

Our next speaker is Dr. Rohit Malhotra from the Division of Cardiovascular Medicine, the University of Virginia.

Welcome.

DR. MALHOTRA: Hi. My name is Rohit Malhotra, and I'm at the University of Virginia. I am a new implanter of the WATCHMAN device and an electrophysiologist. Boston Scientific did pay for my travel here today.

You know, you've heard a variety of perspectives today, and I think I may represent the transition from the physicians to the patients, but I wanted to describe three patients of mine to you.

The first is a 76-year-old man, and he has a history of persistent atrial fibrillation and a CHA_2DS_2-VASc score of 3. He has a HAS-BLED score of about 3 or so as well. He's had an ablation, and it was complicated by some post-procedural pericarditis as well as significant thrombocytopenia that remained undetermined in its etiology. Over the course of a year or so after his ablation, he underwent splenectomy in order to treat this ITP and has subsequently required chronic therapy to maintain his platelet levels at a reasonable level. He's had to undergo platelet transfusions as well as other transfusions in order to maintain adequate counts, and throughout that time he's been very eager to prevent stroke as well. So, despite getting medication to maintain the elevated platelet levels, he's actually been

taking warfarin as well. He's very cautious in everything he does because he realizes that, just in his day-to-day activities, he bruises easily and he bleeds. He's been interested in the device and was going to be enrolled and then couldn't be because the device was removed from the market. He did actually undergo, about 4 weeks ago, an attempted left atrial appendage closure surgically, but due to pericardial adhesions, his procedure was stopped and he was discharged. That's part of why he couldn't be here today.

The second is an 83-year-old man who, much like the prior speaker, has a history of persistent atrial fibrillation and then in October of last year had a GI bleed requiring ICU admission. Unbeknownst to me, this was his second GI bleed. He's doing well. He continues to swim about a mile on a weekly basis, but has been very anxious about his stroke risk as well, and at 83 underwent -- elected to undergo left atrial appendage closure with a surgical procedure that required about a 4- to 5-day hospital stay rather than an overnight admission to the hospital.

The last is a patient who actually I used to take care of before we actually became a WATCHMAN center. He was a patient who had been diagnosed with atrial fibrillation a while before I started seeing him. He lived in Florida and New York and apparently had a nosebleed prior to my seeing him. He had been doing very well in the year or so that I had seen him prior to another nosebleed that required admission to an outside hospital. He then got transferred to our center, where he spent about a month or so in the medical intensive care unit with continued issues. He spent, in total, a grand total of about 3 months in the hospital and subsequently died of his nosebleed. At that point, the options of left atrial appendage closure weren't available to us at all, and potentially that would

have been something that would have prevented his catastrophic death from what we ordinarily would consider a minor bleeding event.

I think the struggle that I've heard all day today has been sort of how muddy the waters are. And, in part, what ends up being so challenging is these trials were all done with standard of care. But the patients I've described and the patients that you'll be seeing can't tolerate that standard of care, and so we don't currently have really much in the way of options for them. These people are all healthy at home, many of them, until one small catastrophic event takes them away. With that I ask for some options.

Thank you.

DR. PAGE: Thank you very much.

Our next speaker is Dr. Zoltan Turi.

Dr. Turi, welcome.

DR. TURI: Thank you, Mr. Chairman and distinguished Panel. My name is Zoltan Turi, and I'm Professor of Medicine and Director of the Structural Heart Program at Rutgers Robert Wood Johnson Medical School. I have the privilege of speaking today on behalf of the 4,000 physician member Society for Cardiovascular Angiography and Intervention (SCAI), founded in 1978 by the pioneers of our field.

I am a practicing interventional cardiologist with nearly 30 years experience in structural interventions. While I had the opportunity to deploy one of the first WATCHMAN devices in the U.S. and was a principal author of the PROTECT AF trial 5 years ago, I have no conflict of interest of any kind to report.

Attention today is focused on preventing a major complication of AF, namely

thromboembolism, and while anticoagulation is the standard of care, it is in itself an iatrogenic disease. Warfarin use is challenging, and the time in therapeutic range has proven to be low, even in rigorously followed patients. The NOACs have shown some superiority to warfarin, but with significant bleeding risk and other issues, including cost and lack of reversibility. For all anticoagulants, patient intolerance, need for discontinuation, or refusal to take over long periods has resulted in substantial under-treatment of this population, with the consequence of often devastating embolic events. Thus, there is a tremendous unmet clinical need to prevent stroke.

Despite extensive ad hoc surgical experience in competing percutaneous technologies, most of what is known about left atrial appendage occlusion and all of the high-level evidence base has been provided by PROTECT AF and PREVAIL, and virtually all of the registry data are WATCHMAN studies as well. SCAI believes the extensively studied patients in the two randomized trials and the CAP registry demonstrate both reasonable safety and efficacy. The fact that this is the third Panel hearing in 5 years highlights multiple issues, which have already been covered today. Although the randomized studies and most of the registry data examined only warfarin-eligible patients, LAA closure technologies are primarily used outside the U.S. in patients with reasons to avoid chronic oral anticoagulation.

The European Society of Cardiology guidelines specifically declare LAA occlusion to be indicated for patients at high risk of thromboembolism with contraindications for long-term anticoagulation, and they cite two references, the PROTECT AF trial and the CAP registry, neither of which directly studied this population but both of which provide insight

into the applicability of the WATCHMAN for this indication.

While no randomized studies have been reported for warfarin-ineligible patients, with 1877 patients enrolled in the WATCHMAN protocols, 5,931 patient-years of follow-up, and an imputed reduction in ischemic stroke of 65% to 81% when compared with historical placebo rates, SCAI feels there is strong evidence that the WATCHMAN device can help address this major unmet clinical need.

SCAI believes there is a compelling need for more treatment options for this patient population than either anticoagulation alone or devices used off label with a very minimal evidence base. We recognize that a randomized comparison of WATCHMAN versus placebo or antiplatelet therapy for warfarin-ineligible patients might have appeal from a clinical trial perspective; however, we believe that such randomization would have major ethical and practical challenges in light of the existing WATCHMAN data. SCAI's position is to recommend approval of the WATCHMAN for patients with reasons to avoid chronic anticoagulation, while mandating additional data collection and analysis to help establish best practices, enhance quality improvement, identify anomalies, and establish the causes of adverse events.

In conclusion, we appreciate the opportunity to provide input to the FDA and the Advisory Panel, and we hope the Panel and the FDA will allow the cardiology community to help this significant and vulnerable population.

Thank you.

DR. PAGE: Thank you very much, Dr. Turi.

Our next speaker is Rose Peterson, RN.

Welcome, Ms. Peterson.

MS. PETERSON: Good afternoon. My name is Rose Peterson. I am a cardiac registered nurse and a research coordinator at Minneapolis Heart Institute in Minneapolis, Minnesota. Boston Scientific did support my travel here, but I'm here on my own free will and nobody is paying me to be here.

The reason I am here is I'd like to briefly speak on behalf of the individuals who have contacted various healthcare providers, who have then referred these individuals to our clinic. These individuals have requested to be placed on a waiting list to receive the WATCHMAN device when it becomes available. Currently I have 52 individuals waiting for the WATCHMAN device. I've chosen three brief stories of why these individuals have chosen to be on the WATCHMAN waiting list. These stories represent the majority.

One: Taking warfarin has caused me not to run or ride my bike like I used to. I'm afraid I may overdo it and cause internal bleeding.

Two: Taking Coumadin causes me to be more dependent on my family and friends. Due to sight issues, I can no longer drive. How would you like to bother someone to take you to the nearest clinic to have your blood work completed? The nearest clinic to me is 45 minutes away. Therefore, it's asking someone to take half of their day to drive me to a 10-minute appointment to have my PT and INR done. This sometimes happens to be weekly. I just want an alternative.

Number three: I'm ending with a heartwarming story from an 86-year-old widowed North Dakota farm wife who spent over an hour on the phone with me explaining why she wanted the device. I've shortened the story. I'm 86 years old and reside on my farm. This

farm has been owned by my family for over 60 years. I still plant, harvest, and can my own vegetables. I drive myself wherever I want to go. Our farm has supported a son and two grandsons through med school. Now I'm told I can't take Coumadin. As like the mice, I bleed internally. I also can't take aspirin, as I have blood in my urine. I want to be able to have the opportunity for an alternative. My fourteenth great grandchild is due around Christmastime, and I want the gift of being here to meet him.

Thank you very much for your time.

DR. PAGE: Thank you very much, Ms. Peterson.

Our next speaker is Dr. Harry Olson.

Welcome, Dr. Olson.

DR. OLSON: Good afternoon, distinguished members of the Panel and guests. My name is Harry Olson, and I am supported in my travel by Boston Scientific to this meeting, but I'm not being paid to be here today.

I am very grateful for the introduction that came to me about a year and a half ago of the WATCHMAN device. In the year 2000, I was diagnosed as having a clogged artery and a stent was put in, and also accompanying that was the medication warfarin. And for 13 years I had two additional stents put in and also a carotid artery surgery. And after those 13 years, what I had to show for it were scars and bruises on my arms and a constant concern of having my blood measured in a timely fashion, and I kept my diet and intake within a reasonable range.

In May of 1913 [sic], I became very weak and was admitted to the Minneapolis Heart Institute and Abbott Hospital and declared that I had, among other things, anemia. After a

consistent number of tests, they could not find any area in which I was having the blood and the bleeding. They took all kinds of stomach x-rays, x-rays of other parts of my body, and came to the conclusion that they were unable to identify where the bleeding was coming from. And so the final conclusion was that my cardiac team suggested that they eliminate all blood thinners and blockages from my care and let nature heal itself.

Two weeks after I was discharged from the hospital, I received a call and invitation to come back for a consultation, and in that consultation they told me about the WATCHMAN device, what this product was intended to do, and gave me a lot of confidence because in my work I'm an ordained clergyman. I also have a master's degree in business administration and a Ph.D. in behavioral psych. I travel worldwide, working with individuals and groups, in terms of resolving conflict, both for profit and nonprofit organizations, and I know that with that in the back of your mind and having to take all of that medication in a timely manner, it was challenging to the work that I had to do, to the people I worked with, and to our opportunities.

And so I want to tell you today that with all sincerity, I may not have been here today had it not been for the WATCHMAN. And may you take into mind the fact that we cannot take away from the public a cure, an answer to a dream that's been given to us through this device. So believe in yourself and in your plan. Say not I cannot, but I can. The goals in life we fail to win, only when we doubt the power within.

Thank you very much.

DR. PAGE: Thank you very much, Dr. Olson.

Our next speaker is Dr. Herbert Floyd from Rush Medical.

DR. FLOYD: Thank you. I'm Dr. Herbert Floyd. Boston Scientific is paying for my travel expenses, but I have no other financial interest.

I am an emergency physician in rural Mississippi. I was at work on June 8th of this year when I began to have weakness in my right side and I had a hemorrhagic stroke, which caused me to have severe weakness, particularly in my right hand. I couldn't even clench my fist. So I was airlifted to a large -- I work in a very small hospital. I was airlifted to a large hospital in south Mississippi, and I was in ICU 2 days, and I was in neuro rehab for about 3 weeks total in the hospital.

My speech was not affected very much, and I was able to walk pretty well, but I still had profound weakness in my right hand, which I can't work as an ER physician with a weak right hand. There are procedures that I can't do. So with intensive physical therapy for two and a half months, I was improved a great deal, and I've actually been able to return to work on September the 1st. But my neurologist will not allow me to take any further blood thinners. He said the risk is too great that it might next time be a much worse outcome. But I still have chronic atrial fibrillation, so I'm at risk for an ischemic stroke, and that's a fearful thing. Going through the first stroke was bad enough.

But considering this, I'm scheduled to go to Vancouver, Canada next week, and I'm going to have a WATCHMAN device implanted. I don't really see any alternative. I want to live to see my children and grandchildren grow up, and I want to live without the fear of an ischemic stroke, and I think that this will fit the bill more than anything else, and I urge you to approve this for patients like me.

Thank you.

DR. PAGE: Thank you very much, Dr. Floyd.

Our next speaker is Stephen Stanko.

Welcome, Mr. Stanko. And, sir, I'm afraid you won't be able to see the yellow light where you're sitting, so we might ask -- I'll raise my hand when we're getting to that, to the 3-minute --

(Off microphone comment.)

DR. PAGE: Oh, you have it there. Great. Okay.

MR. STANKO: Good afternoon. My name is Steve Stanko, and I am a retired marine, Purple Heart veteran. Boston Scientific supported my travel, but I have not been paid for my time to be here today.

Since 1984 I've had five heart attacks, two open-heart surgeries, three PCI procedures, a sudden cardiac death, and three AICD implants. I have had continuous A-fib for nearly 4 years, and I have been in the Coumadin clinical trial under investigator Dr. Saibal Kar for over 3 years. Because of my weakened heart, I suffered the facial droop that accompanies stroke during a PCI session in the late 1990s but returned to normal while I was still in the cath lab. I made my doctor smile when I was able to show him my teeth. I began Coumadin as a stroke countermeasure after this PCI. I was on a high dose, and my clotting time was not under control. I awoke one morning with no vision in my right eye. My INR had spiked, and I had bled into the fluid of my eye. I stopped the Coumadin and was wary of using it again but regained my vision after a month.

I withstood three silent heart attacks without Coumadin until my sudden cardiac death in April 2001. After recovery, I received my first AICD and did quite well, rebuilding

my strength and using amiodarone to control my A-fib. I continued to do well until late in 2009 when medication for a thyroid problem made my A-fib untreatable and necessitated oxygen 24/7.

I went to Cedars-Sinai in July 2011 to inquire about the WATCHMAN. I learned about the clinical trial, joined the trial, was evaluated and was randomized into the Coumadin leg. I recently passed my third year on the drug and have become thoroughly familiar with all of its disadvantages. During the evaluation, the Cedars staff determined that I would do better with a biventricular ICD. I stopped Coumadin for 5 days and had the device installed in September 2011. The implant was complicated and required an 8-day stay until I recovered and my INR regained a therapeutic level. During recovery from surgery, I suffered three pleural effusions and had to stop Coumadin for 5 days, each time to drain my left pleura. I bruise quite easily, and minor taps to any extremity produced severe skin blotches. My dog causes many skin irritations as she tries to love me with her paws. Daily nose bleeds result from the oxygen cannula and the high clotting time. Clots are easily dislodged to bleed again. A week-long bleeding and three hospitalizations accompanied a routine colonoscopy, even with the 5-day Coumadin break.

The 3-year wait for the FDA approval of the WATCHMAN has been tortuous. I ask that you please consider the benefits of this alternative to Coumadin and approve the device.

Thank you for your time.

DR. PAGE: Thank you very much, Mr. Stanko.

Our next speaker is Lawrence Loughnane -- Dr. Lawrence Loughnane.

Welcome, sir.

DR. LOUGHNANE: Good afternoon. My name is Lawrence Loughnane, and I am currently -- I don't know how to change the slide. I am a participant in the evaluation of the WATCHMAN. I am a patient at the Division of Cardiovascular Diseases at the Scripps Clinic in La Jolla, California. I'm here to let you know how the WATCHMAN device has changed so that I can live my life. Not just life, being alive, but my life. Boston Scientific has paid for my travel, but other than that, no obligation.

But to know what the WATCHMAN device has done for me, let's know a little bit about me, what I was --

DR. PAGE: Sir, if you can look this way. When you turn to that side, we lose you on the microphone.

DR. LOUGHNANE: I apologize.

I joined the navy when I was 19 years old. I spent a career in a submarine force. It was cut short after 15 years. I was medically discharged in 1975. It didn't slow me down. I went off to a career in business. I worked for big companies and small companies, for the government. I was a vice president of West Coast operations, owned my own business and ultimately an international consultant, traveling from here to Mexico, to Ireland, to Spain, to the UK. At age 50, I reinvented myself. I went back to graduate school and obtained a Ph.D. in 1998 at age 55. I was an Energizer bunny. I worked as a consultant, like I said, for the Irish government, Mexico, Spain.

In 2000 I had a heart attack and was airlifted out of the Grand Canyon. I was hiking in the Grand Canyon, running up and down stairs. They did an emergency heart surgery in

Phoenix in 2000. I returned to work in November 2000 and was in Ireland visiting the Irish government in December of 2000. In 2007 I had six stents. All four of the grafts that I had for the bypass failed. One failed all the way. They put two stents in each of the remaining three. In 2010 I had my second quadruple bypass surgery, and then the A-fib started and I went on Coumadin therapy. I tried to resume my international work. My work just suffered. I couldn't work. I was constantly worried about my INR. One time I was in Spain and I had my INR tested -- it was hard to find somebody to do that -- and it was at 5.8. I had no alternative but to stop the Coumadin therapy. My life was pretty much gone.

And then along came -- you can see the snapshot of my life. I was, like I said, the Energizer bunny. I was off doing a lot of things. I was a writer, I was a researcher, I would go to conferences. But I couldn't do it anymore. I just couldn't do it. I was contacted by Dr. Matthews from Scripps. He introduced me to the WATCHMAN. I read the research myself. I went in and got as much information as I could that was public domain, and I looked at it and I said the risks, based upon a benefit for me --

DR. PAGE: Thank you very much, Dr. Loughnane. We'll have to move on to our next speaker. Thank you.

Our next speaker is Wilford Brimley.

Welcome, Mr. Brimley.

MR. BRIMLEY: How are you doing? Everybody okay? I ought to give my time to some of these guys that got a better story. I was taking that rat poison and didn't like it. My life was not much fun. I've been an outdoor guy all of my life, and I was a horseshoer professionally -- a horse trainer. I went to a rodeo now and then. And when I got this

irregular heartbeat, a guy told me, "Well, hell, if you fall off your saddle horse, you're liable to lay there and bleed to death." Well, I didn't like that.

So I went to a heart doctor in Salt Lake City. A good guy. He said, "How old are you?" And I said, "Oh, 71 or something like that." He said, "Well, if I was you, I would just keep taking the Coumadin and ride her on out." And that's what I was going to do. And then I was introduced to a young fellow in the same city, in the same group, who said, "I may have something better to offer you." And all the medical data and all of that stuff these fellows are talking about is Greek to me. But I looked this kid in the eye and I said, "Listen, if this was your dad, would you have him do it?" He said, "You bet." So I did.

Blow your whistle any time, because if I talk about myself over 4 minutes, I'm lying.

(Laughter.)

MR. BRIMLEY: My life is better, and I'm just going to take one minute to tell you about some of the shit you have approved. You watch the television and they'll say, here, take this in place of that, this in place of that, but see your doctor first because it will give you moles, farts, and freckles and make you want to kill your mother while you're having diarrhea.

(Laughter.)

MR. BRIMLEY: Well, I don't want to take that stuff, see? I went from 16 pills down to 2. I take one for my cholesterol and I take -- oh, what the hell is the other one? That don't matter, but it ain't 16.

God bless you all. Oh, I forgot to tell you. Somebody bought my ticket here. I don't really know who --

(Laughter.)

MR. BRIMLEY: -- but I'm not being paid. The way they paid me was to give me back my life.

DR. PAGE: Thank you very much, Mr. Brimley.

Our next speaker is Patrick Robins.

MR. ROBINS: Hi. I am Pat Robins. I can't keep up with our previous speaker. That was wonderful. Boston Scientific supported my travel here today and not my time, and I have no financial interest in the company.

I am a 76-year-old guy living in Burlington, Vermont, and I stay active as a board member of several corporations and nonprofit organizations, and I'm the owner -- principal owner and chairman of a regional technology services company. I stay active and deeply involved in community affairs, and I continue to work somewhat futilely on my golf handicap.

Unfortunately, or perhaps fortunately, in March of 2011, I was diagnosed with coronary artery disease, and Fletcher Allen cardiologists implanted three stents in my 80% to 90% blocked arteries. I subsequently joined their excellent cardiac rehab program and got in shape and lost 25 pounds. I got my blood pressure and bad cholesterol down to the target numbers, admittedly with the help of a pack of medications. A year later, while vacationing in Barbados, I suffered an occipital stroke that fortunately caused only a minor residual visual impairment. As is often the case with strokes, I was soon thereafter diagnosed with atrial fibrillation and was prescribed the anticoagulant Xarelto, with the goal of avoiding another A-fib related stroke.

As I studied online to better understand my situation, it became clear that the risk of a serious, even fatal, bleed related to anticoagulants increases with each year of use and at some not too distant point becomes greater than the risk of a stroke itself. I became concerned and started to ask about some options. I was referred to Dr. Daniel Lustgarten, my friend here in the back, the principal investigator of the WATCHMAN studies, then ongoing at Fletcher Allen in Burlington, to discuss whether I might be a candidate for the WATCHMAN implant. He described the theory and promise of the device, cautioning me that the program was experimental, that there would be a wait to get it implanted, and that the protocol required me to switch to Coumadin, an alternative anticoagulant that required more management during my daily routine. Nonetheless, I readily agreed.

But as the A-fib became more frequent and intrusive, Dr. Lustgarten recommended and performed an AF ablation, which has been, to all appearances, very successful. Nonetheless, with my high $CHADS_2$ score it is clear that a patient like me needs a life-long stroke-mitigating strategy. It was my great fortune to just make it under the wire for the CAP2 registry at Fletcher Allen, the protocol for which mandated that I continue to take Coumadin until the WATCHMAN implant was complete and declared successful.

So, in March of this year, Dr. Lustgarten and his team successfully implanted the WATCHMAN device. I found the procedure and post-procedure period to be somewhat less intense than that which I experienced with my ablation. The subsequent TEE showed the device had completely blocked the atrial appendage as intended, and I was cleared to stop taking the anticoagulant in May, to my great relief. During the 2 years that I took the anticoagulants, due to my fear of falling, hitting my head, and starting a potentially fatal

bleed, I had given up any but the most essential winter walking, fearing the icy conditions that are a status quo in our neck of the woods, and stopped hiking on steep trails and riding my bike. Any number of other activities I normally considered routine suddenly posed significant risk and greatly limited my previously active and rewarding life. The WATCHMAN has given me back all of those activities and more.

While none of us with or without high $CHADS_2$ scores can be certain of avoiding strokes, I'm confident that the WATCHMAN blocks the source of nearly all the strokes affiliated with A-fib at least nearly as well as blood thinners, and the device has greatly enhanced my life by removing the threat of complications associated with the latter. I urge you to approve its use for all similarly afflicted Americans.

Thanks so much.

DR. PAGE: Thank you very much, Mr. Robins.

Our final speaker is Richard Maheu. And I apologize if I mispronounced your name, sir.

MR. MAHEU: Well, you got it pretty close. It's Maheu.

I want to thank the Panel for giving me a few minutes to speak. I am the patient the doctor was referring to that had a GI bleed about 6 weeks ago. Up until that time I had a pretty normal life. My business grew, and I ran two dental companies limited to endodontic surgery. We were a niche company, but we did business in 55 countries. I sold those to a public company about 10 years ago, mainly because of the increasing fear of being overseas and out of the country for a potential GI bleed.

Going to the beginning, I think -- I'm not exactly aware, but I think my airplane ticket

was paid for and my stay, but I have no financial relationship with any company.

In 1996, at the age of 48, I had a heart attack and subsequent bypass surgery and within a week an implanted defibrillator. So I've been dealing with the long-term effects of Coumadin and warfarin for approximately 18 years. I live in A-fib, therefore at a high risk of stroke. It is my belief that the WATCHMAN would change my life and give me back many of the freedoms and activities that I had before.

I've had my ups and downs with Coumadin over the years, mostly good experiences. However, I elected to have simple bunion surgery July 30th of this year. It seems like a long time ago, and this is October. That wound should have healed, but recovering, I had a GI bleed. So I had three transfusions of blood, and when I was released from the ICU, my blood count was 7.7 and it should be around 13, 13.5. So it sort of frees -- Dr. Sanchez -- and since the wound is not healing, it's subject to infection, and Dr. Sanchez has recommended, along with other doctors, that I go to a wound clinic. And in talking to them about different cultures that are growing in the open wound, one of the things that came up was *Staph* infection.

The drug was flagged that they wanted to deal with with *Staph* infection, because it doesn't do well with Coumadin. So, in a conversation just 2 days ago, I heard four times, we're stuck, we're stuck. We can't do what we need to do. So I was happy, in a way, to receive the news 2 days ago that they decided that the risk of stroke is worse than the risk of bleeding. You can replace blood, but maybe not a stroke. So now, for the last 2 days on that medicine -- and I hope to get not only my strength back, but the wound on my foot, which is ridiculous -- after two and a half months, it's still open and not healed.

I know all of you people are very busy. I don't dwell on the fact that I'm in a category of high risk. And I try not to read the obituaries too much, but there is a category that catches my eye when reading them. And if you're relaxing on a Sunday, you might want to just read it and says died of complications of heart failure after a long illness, a long illness of chronic heart failure. That's a column that you guys can eliminate. Like an elite club, it's not one that I want to be in.

And I thank you for your time.

DR. PAGE: Thank you, Mr. Maheu, very much.

At this point I'll ask the Panel if any of you have any questions for the Open Public Hearing speakers.

(No response.)

DR. PAGE: Seeing none, I will pronounce the Open Public Hearing segment to be officially closed.

I do want to thank the speakers very much. For one thing, you stayed on time, and I appreciate that, and it allowed us to hear every voice that wanted to speak. I also assure you that we really listen to you, especially the patients. I know a number of you have traveled from a distance to be here, and it means a lot to us, and we will certainly be considering your input as we deliberate and try to find what we think is the right thing to do here.

So with that, we'll proceed with today's agenda. We will now begin the Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all

persons who are asked to speak identify themselves each time. This helps this transcriptionist identify the speakers.

Now, Nicole Ibrahim from the FDA has been keeping up with the questions that we had, and we didn't have that many this time.

Ms. Ibrahim, would you please remind us of the questions, I believe, that were posed to the Sponsor?

DR. IBRAHIM: There were a couple of questions that were posed during the two question and answer sessions. The first question was related to the hemorrhagic events, patients with the hemorrhagic events, and whether they were on antiplatelet therapy at the time.

DR. PAGE: Dr. Stein.

DR. STEIN: I can answer that. I'd also just ask, Dr. Page, the Chair's permission. In addition to the questions that we had asked, there were also two other questions that were addressed to FDA that I believe we can provide some clarifying comments on, if that is all right.

DR. PAGE: That's fine.

DR. STEIN: Good. So let me begin, then, maybe with the two to clarify just -- or stay on the other questions.

DR. PAGE: Let's address the questions as the FDA is putting them forward, please. Just in order. Thanks.

DR. STEIN: Great. So this was the question regarding which patients were on concomitant antiplatelet therapy at the time of their hemorrhagic stroke. In PREVAIL, both

of the patients who experienced hemorrhagic stroke were on aspirin in addition to an anticoagulant at the time of the event. In PROTECT AF, of the 10 warfarin patients, at least 4 were on aspirin at the time of the hemorrhagic stroke. But as Dr. Farb noted, the data is not always clear from source documentation. I think it was discussed earlier today, you know, that putting these patients on aspirin may have been an error on the physician's behalf. But I'd emphasize that I think these data show that in the set of patients with multiple comorbidities, many of whom had prior coronary intervention, peripheral arterial disease, et cetera, that there's a large requirement for concomitant antiplatelet therapy for primary or for secondary prevention.

DR. PAGE: Thank you.

DR. IBRAHIM: There was a request for clarification on the number of deaths in one of the tables presented in the PREVAIL data and clarifying the reasons for the deaths.

DR. STEIN: Yes, we can pull it up. This is our Slide AA-5, if you'd pull that up, please. And I want to thank Dr. Page for pointing out our math error. I'm sorry. Actually, it was Dr. Lange who pointed it out. I can thank both of you, but --

DR. LANGE: My math is better than Dr. Page's.

(Laughter.)

DR. STEIN: -- particularly thank you, Dr. Lange.

As I mentioned in response to one of the other questions this morning, there was one re-adjudication of an event. There had been a patient in the PROTECT -- I'm sorry -- in the PREVAIL WATCHMAN arm who had a hemorrhagic stroke that was followed by death, and as I said, the CEC had initially adjudicated that as not being a cardiovascular death.

And, again, just as we were preparing for the Panel, we were uncomfortable with that, and so they re-adjudicated it as both a hemorrhagic stroke and a cardiovascular death. And so that is included in here as the one. We inadvertently did not update the total at the top eight, so the total should have been nine. This is the updated total with the updated rates and statistics. We have gone through all of the rest of the data that we presented to you today, and for all of the rest of the data, we had accurately updated the totals to reflect that re-adjudication. And I thank you for pointing out the error.

DR. PAGE: Thank you.

DR. IBRAHIM: The next request was for additional data on the ejection fraction between the control and device groups.

DR. STEIN: Yes. And I think we were asked both in terms of the distribution -- you know, were the ejection fractions different between control, and then was there a subgroup analysis to look if that affected outcomes. And so to begin with, it's our Slide AA-8. So for the pooled analyses, this shows the comparison of the ejection fractions for WATCHMAN and the warfarin patients and you see they are essentially identical. I can go ahead and show the pooled data and look at the subgroup analysis by ejection fraction.

And so this again is out of the pooled meta-analysis data, looking by subgroup ejection fraction dichotomized at 55. I think it's important to clarify to the Panel that the patients could not enter the trials if they had an ejection fraction below 30%. So there's a group between 30 and 55 and then a group of ejection fraction above 55%, and as you see, there's no statistical evidence of any heterogeneity in outcome. In both groups, the point estimate of the hazard ratio is to the left of 1, favoring WATCHMAN. I think there also may

be some interest in whether this affected, in particular, the individual endpoint of cardiovascular or unexplained death. So, with your permission, I can show that analysis as well.

DR. PAGE: Ms. Ibrahim, have we already covered these questions?

DR. IBRAHIM: There's one additional question.

DR. PAGE: Okay, let us just finish with the questions, then I'll make sure to give you that opportunity at that time.

DR. STEIN: And I'd come back to it.

DR. PAGE: Yes.

DR. STEIN: Absolutely.

DR. IBRAHIM: So the last one is actually more of a clarification. There was a table presented on major bleeding in PROTECT AF, and there was a request to sort of check the event numbers that are listed in that table.

DR. STEIN: Yes. And there had been 52 total events if you summed the rows, but 50 individual patients with events. And, Dr. Page, I think you were the one who speculated that it was because of two patients who were in both rows, and you're right. So it's 50 individual patients who experienced events. There were two who had experienced both a procedure- and a non-procedure related event.

DR. PAGE: Great. So that summarizes and we've completed the questions that we had remaining from before the lunch break?

DR. IBRAHIM: Yes.

DR. PAGE: Great. Thank you.

And now, Dr. Stein, why don't you go ahead and respond to the questions that we had -- at least you thought we had implied that we wanted an answer to --

DR. STEIN: Sure.

DR. PAGE: -- and present those data.

DR. STEIN: So let me begin. I should go back to the left ventricular ejection fraction breakdown, just to complete that story while it's fresh. And so, again, we showed you that the ejection fractions are comparable between the randomized groups. We showed you that there's no heterogeneity with respect to the composite endpoint of stroke, systemic embolism, or cardiovascular or unexplained death.

Just in terms of thinking through the question and perhaps the motivation behind the question, we also looked at whether there's any difference in the individual endpoint of cardiovascular or unexplained death attributable to baseline cardiovascular risk factors, including left ventricular ejection fraction. And so this slide shows you the results of the subgroup analysis, and you see again that, broken down by ejection fraction or, in fact, broken down by other cardiovascular risk factors in all groups, the point estimate of the hazard ratio for cardiovascular or unexplained death is to the left of unity and that there is no significant interaction based on either prior history of coronary disease, prior CABG, prior MI, prior coronary intervention, or ejection fraction greater than or less than 55.

DR. PAGE: Great. Thank you.

DR. STEIN: And I thought the two points -- again, with your permission, I thought you did ask for some clarification in terms of how they were asked of the Panel and FDA, but I think we can provide a little more background on them.

There was a question of whether PREVAIL, at 860 patient-years, is powered and in the context of PROTECT AF, being initially presented at 900 patient-years. So we reviewed this with our statisticians, and we do not believe the 860 patient-year analysis of the PREVAIL-only data is adequately powered. PREVAIL was designed only for its pre-specified Bayesian analysis.

So why could PROTECT AF be presented at 900 patient-years? So PROTECT AF was presented at 900 patient-years as part of an appropriate pre-specified sequential analysis plan, but it was not initially anticipated that 900 patient-years would be adequate. And, in fact, those of you who recall that 2009 Panel may recall that one of the concerns expressed at that Panel was that 900 patient-years of PROTECT was not sufficient to make robust conclusions about device safety and efficacy. And, in fact, the Panel in 2009 requested additional follow-up in PROTECT, and that's what we presented at 2013 and then updated and presented again today. And, of course, the most power is obtained when you look at all of the studies in totality.

Second, I think there was some back-and-forth with the Panel with discussion, just as there was in 2013, about the Bayesian analysis, both the mechanics of the Bayesian analysis and the rationale of the Bayesian analysis. And, again, those of you who were here in 2013 may recall that at the time, there was a request to present pooled data in a frequentist fashion rather than a Bayesian fashion, and that was our motivation behind presenting again today the pooled data in purely frequentist terms.

DR. PAGE: Just so I'm clear, when you're talking about pooled data, are you talking about the meta-analysis?

DR. STEIN: So I'm talking right now about the meta-analysis.

DR. PAGE: Okay.

DR. STEIN: And that is just the pooled randomized trial data, yes.

DR. PAGE: Thank you. Yes, please go ahead.

DR. STEIN: Great. And, again, back then we were asked to pool the data because both trials studied the same device, because both studies had the same control and because both had the same primary outcome measure. For purposes of the meta-analysis as I'm showing you now and as we presented this morning, we did stratify the analysis for differences at the individual study level to account for differences in the baseline inclusion criteria and baseline risk.

I did have a sense again, in some of the questions, that there may still have been some concern. And so if there is still some concern about that pooled analysis, we can show you the same type of meta-analysis, but only including, in addition to PREVAIL, the subset of patients in PROTECT who would have been eligible for PREVAIL. Instead of adjusting for baseline differences by stratification, all right, we adjusted for baseline differences by including only, for this pooled analysis, the patients in PROTECT who would have met the more strict entry criteria for PREVAIL. And so that would be the result of this meta-analysis.

And I think really the major point that I would like to make here is it's not substantially different from the other meta-analysis, that is, the hazard ratio for efficacy at 0.81 still shows that the device is comparable to warfarin for the combined endpoint of all stroke, systemic embolism, or cardiovascular death. It actually looks a little bit better in

terms of the all stroke rate. The hazard ratio is 1.00 instead of 1.02, so exactly comparable numbers of all stroke. There is still an excess of ischemic stroke in the WATCHMAN group relative to warfarin, but there is still a large excess in hemorrhagic stroke in the warfarin group compared to WATCHMAN, and there is still a statistically significant advantage for WATCHMAN in terms of cardiovascular or unexplained death.

DR. PAGE: Well said. Thank you, Dr. Stein.

At this point I'll ask the Panel if they have any questions. And if I may, I'll first address our Patient Rep and our Consumer Rep, Ms. Chauhan and Ms. McCall.

Ms. Chauhan, do you have any questions for either the Sponsor or the FDA at this time, ma'am?

MS. CHAUHAN: Not at this time. Thank you.

DR. PAGE: Thank you.

Ms. McCall, do you have any questions for either at this time?

MS. McCALL: Not at this time. Thanks.

DR. PAGE: Okay, thank you.

And, Mr. Thuramalla, do you have any questions for the Sponsor or the FDA at this time?

MR. THURAMALLA: Yes, I have one.

DR. PAGE: Go ahead, please.

MR. THURAMALLA: Looking at the FDA slides that show a significant divergence of the performance between the PREVAIL data and the comparison -- so these points are to clarify on what data analysis was to show that it was superior in many of the other

categories. I can reference the slide numbers if you wish.

DR. PAGE: I think that it would be helpful if you reference what number slide and who presented the slide. And, again, you're asking this of both the FDA and the Sponsor?

MR. THURAMALLA: I'm asking the Sponsor --

DR. PAGE: The Sponsor. Okay, thank you.

So, Dr. Stein, I'll ask you to respond when we get this up.

MR. THURAMALLA: So the FDA slide which talks about the summary is Slide Number 153. It reads, "The updated data shows significant divergence between PREVAIL outcomes to the PROTECT AF prior."

DR. PAGE: Okay, and let's get that up. And again, can you give us the title again, because the numbers got off by several by the end of the presentation.

MR. THURAMALLA: So the title of Slide Number 153 from FDA is called "Updated PREVAIL Study – Summary of Bayesian Analysis." And Slide Number 75 from the Sponsor, which calls out -- the title of which is "WATCHMAN Comparable Alternative to Warfarin." It indicates in several of the cases that it's superior to warfarin. So I wanted to clarify the rationale behind the divergence of performance in the context of superiority.

DR. NEUBRANDER: I'm sorry, could you repeat the FDA slide number one more time?

MR. THURAMALLA: It's Slide Number 153.

DR. NEUBRANDER: Okay.

DR. PAGE: And was that the 153 that was projected or the one in your Panel pack?

MR. THURAMALLA: In the Panel pack it is 142.

DR. PAGE: Okay.

DR. NEUBRANDER: The title again?

MR. THURAMALLA: "Updated PREVAIL Study – Summary of Bayesian Analysis."

DR. STEIN: Okay, thank you. That's the slide. Yes, good. So I think the question of whether there's a true divergence in device performance across the trials, in particular between PROTECT and PREVAIL, is certainly one that the Panel is going to be considering. I'm going to invite Dr. Reddy up to address the issue of whether there actually is a divergence and if there is, what would be the mechanism. And I think we need to -- how do we switch back to our slides? We got it.

DR. REDDY: Thank you. Vivek Reddy, Mount Sinai Hospital.

Let me just go through a couple of points. The first is this slide. I showed this in the core presentation. What you're looking at here again is the primary efficacy endpoint: stroke, embolization, and cardiovascular death. And as you look across the various trials -- and here you're looking again at just the WATCHMAN arm performance in these various trials -- you see that there's not much difference once you account for the increase in patient risk score, that is, in PREVAIL and CAP you see the mean CHA_2DS_2-VASc score has increased from 3.5 and 3.9 in the first two trials to 4.0 and 4.5 in the second trials.

DR. PAGE: May I just interrupt for one second? It says primary efficacy rate per 100. Is that primary event rate?

DR. REDDY: Yes, it's the primary event rate. That's correct. So this is stroke, embolization --

DR. PAGE: These are bad things happening and not good things?

DR. REDDY: That's correct.

DR. PAGE: Okay.

DR. REDDY: That's correct. But the point I'm trying to make is when you look at the WATCHMAN device performance, how that arm performed. If you look across trials, there's not a significant difference once you account for this. And I started with this slide because I do believe it's important to look at the primary efficacy composite, not just the individual components, because when you start tearing this up into individual components, you have smaller numbers and it becomes more difficult to interpret.

Now, having said that, I do know that we're interested in ischemic stroke, and I just want to point to this slide. Again, this was in the core presentation. And, remember, the dotted line is in the untreated patients, what happens; the solid line is what happened in warfarin-treated patients. What I'm showing here is the ischemic stroke rate, not the composite, just the ischemic stroke rate amongst trials, and what you see is again, once you account for the baseline CHA_2DS_2-VASc score in this case, that the values -- the point estimates straddle the Coumadin line, that is, the device performed as expected.

Now, having said that, we've already seen in our slides and the FDA slides that there is -- that when you look at it as compared to warfarin, for ischemic stroke the WATCHMAN group fared worse. There's no doubt about that. And the reason is there was only one stroke in the control group in PREVAIL, one stroke out of 130 patients followed for 2 years and a CHA_2DS_2-VASc score of 4.0.

Now, I'm not trying to say that because the control group performed so well, you know, that's not fair, we should ignore that data. That's not the point. But the point is I

think, just as it's not fair to ignore that data, it's also not fair to ignore other data. And that was the point of the meta-analysis. I'm not going to go through this again and you've already heard the story, but I do want to just emphasize. The purpose of the meta-analysis was not to try to overemphasize PROTECT nor was it to try to underemphasize PREVAIL, but rather to show all of the data and equal emphasis per patient. And the other thing I like about this particular analysis is that I'm not thinking about Bayesian. I'm thinking in a way that I can understand, which is basically the relative point estimates, the hazard ratios, and a p-value.

And the last point and the last slide I'll show you here is this one. This is a variation of the slide that Dr. Huber showed earlier. What you're looking at here is what would be expected using a 5-year time horizon in the three different possibilities: the WATCHMAN group, the warfarin group, and a group that wouldn't receive anticoagulation. The reason I'm showing this slide is because these are non-inferiority studies and non-inferiority studies, to me, are very difficult to get my hand -- to get a grip on because really when you're looking at a non-inferiority study, you really want to see superiority to prove to yourself that you're really not inferior.

But we've got to remember, the purpose here is not to say that WATCHMAN should replace warfarin in all patients. The purpose here is to say we need an alternative for some patients who are not great candidates for long-term warfarin, and in that context, I think this slide helps. On the far right is what happens if you don't take anything else. Warfarin reduces that, which is why warfarin is an excellent candidate of treating our patients. So, by the way, are NOACs, which looks very similar to warfarin. And finally you see

WATCHMAN, which is in line with warfarin, again as an alternative to long-term anticoagulation.

DR. PAGE: Thank you, Dr. Reddy. Could we actually go back one slide and then the next slide, just because I want to be clear on something because I think it will inform our subsequent discussion? So go back to AA-12, please.

DR. REDDY: Oh, okay. One second.

DR. PAGE: Go back to 12.

DR. REDDY: Yes, it's coming up right now.

DR. PAGE: And I think that, at least to me -- and we'll see what the Panel thinks -- is a fairly compelling kind of line there. But go back to 11.

DR. REDDY: Can we go back to 11, please?

DR. PAGE: I just want to make sure I got the numbers right, because the point you made is that they all fit together. But the Panel can decide whether we need to discuss the fact that you have a 2.2 in PROTECT and a 4.3, almost double, in PREVAIL. I'm not asking you to comment. As a matter of fact, I just want to make sure everybody looked at this in case we want to discuss it later.

Thank you.

DR. ZUCKERMAN: Before you take that off -- because I do think that's a nice summary slide. Could you put it back up, Dr. Stein?

DR. PAGE: And that's AA-11, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. You know, you're calculating these event rates per 100 patient-years, and there are some concerns about how the hazard ratio changes over time.

So with the CAP2 calculation, what is the mean follow-up of the CAP2 patients?

DR. STEIN: Yes, I'll pull that up in just one second. We can show you the demographics and we can show you the mean follow-up in each of the trials. So CAP registry mean follow-up is just barely over a half a year. It's 0.58 years as opposed to, as you see, follow-up in PREVAIL, 2.2 years out to a 4-year mean follow-up in PROTECT.

DR. ZUCKERMAN: Okay. So there is one problem about the hazard ratio changing over time, and I hope that Dr. Naftel can help us interpret an average statistic when we have that problem in the later discussion, one.

Two, is I do believe that there are additional CAP2 events that have not been adjudicated yet fully by the Sponsor and FDA. So, again, it points to Dr. Page's point about how one interprets that summary slide, either liberally or conservatively.

Thank you.

DR. PAGE: Yes, thank you. And thank you, Dr. Stein.

We're going to continue on with the questions. Dr. Furie has been very patiently waiting since before lunch, then Dr. Cigarroa, and I've seen Dr. Lange's hand as well.

DR. FURIE: Thank you.

This is a question for Dr. Stein. It pertains to the information we received that approximately 5% or 6% of patients have thrombus superimposed on the device at 45 days. And you showed a very vivid cartoon of the device becoming endothelialized over time. Can you just share with us the time frame for when that is completely endothelialized and whether you think the late events might be due to incomplete endothelialization of the device?

DR. STEIN: Thank you. I'm going to answer that really in three ways. I think the first point is just a point of clarification. So the thrombus rate that you refer to -- and it's sort of in that 3% to 5% range -- that's not a 45-day rate. That was thrombus on any -- either surveillance TEE or a TEE that was done for intercurrent events. So recall, in the trials, we had surveillance TEEs done at 45 days, and in two of the trials at 6 months, and all of the trials at a year, and then many patients again had a TEE if there was an intercurrent event. So that was a thrombus -- just for clarity's sake, that was a thrombus rate taking into account on a per patient basis, irrespective of time course.

First of all, I think it is important to say -- I'll get to the actual preclinical data and the limited clinical data that we have on endothelialization in a moment, but I first do want to address the issue of whether there is any signal of increased risk of late events. And I can do that in two ways. I think, first, there was a slide that we showed you in our core, where we look at our two largest trials with the longest follow-up, follow-up and number of patients out to 5 years. And just again looking at the Kaplan-Meier curves, you can see that there is not an increased hazard of stroke apparent in this long follow-up of these larger patient cohorts.

I think also this gets to a point that Dr. Zuckerman raised earlier about whether hazard ratios are constant over time or whether they are not. And, actually, it's a very important point to think through, and it's one of the reasons that we used this piecewise exponential model when we did our event modeling for PREVAIL because, in fact, the hazard rates are not exactly constant over time. And I think this came up in the morning. There was a question of whether there was equivalent -- I think Dr. Kandzari asked if there's

a landmark analysis that we did, looking at events over time in the trials, you know, something similar to what we showed for the bleeding analysis. And I don't have that analysis for all of the trials, but I do have that analysis for PREVAIL.

And so what you see if you look at the pre-specified time components of the piecewise exponential analysis where we broke it down to periprocedural, then up to 60 days, which is the time when patients with WATCHMAN are being covered with warfarin and/or dual antiplatelet -- well, mostly with warfarin and some with dual antiplatelet therapy -- then the time out to half a year and then we go out to the time beyond a year, you see the hazard rates do fall, over time, in the PREVAIL trial, and you see that for the late events beyond 182 days, there's no difference in outcomes between the WATCHMAN and the warfarin arms.

And then the last thing I'd like to do is to invite Dr. Holmes up to address the data that we have with respect to endothelialization, both in our preclinical models as well as with some limited human data.

DR. HOLMES: Dr. Page and Panel members, I'm David Holmes, and I'm from the Mayo Clinic in Rochester, Minnesota. It's important to remember that both Mayo and I licensed some early technology to the earliest company involved with this -- in terms of conflict of interest.

As we began this journey a really long time ago, there wasn't very much data on the issue of endothelialization with a device that you would put in for a long period of time. And so one of the first things to do was to say, what do we have in an in vivo experience in an animal model? And so we then began a series of experiments, and as you can see here

in this canine model, when we looked at endothelial cell covering -- lining by 45 days, we found that there was indeed endothelial cell lining that was pretty complete by 90 days without residual inflammation.

We then looked at another series of those and said, well, maybe by 90 days it's not perfect because some of the time at 28 days there were still some areas that had not been fully endothelialized. We need to remember, at that time, that around this we were also putting in devices to close the atrial septum as well as the ventricular septum, and in those patients, we were giving them prolonged anticoagulants for a certain period of time to try to make sure that the device was endothelialized. And so that was part of the process by which we said we should be using 45 days of Coumadin in all of these patients, and that formed the basis for all of the trials.

The final piece of information is that it would be very nice to have more slides like this to show you, but we'd rather not have a lot of slides like this to show you. This happens to be a human heart 200 days after WATCHMAN implantation, and you can see, what we would like to see in everybody would be complete endothelialization of the device.

So the journey was early canine experiences where we looked at endothelialization that was somewhere between 30 days and 45 or 60 days, and that was then the basis of adding warfarin to this to make sure that that was optimized.

DR. PAGE: Thank you, Dr. Holmes.

Next, I'll call on Dr. Cigarroa. Do you have a question for the Sponsor?

DR. ZUCKERMAN: Dr. Page, could the FDA just respond for a moment to Dr. Stein's excellent points? And then BSC can have the final word here.

DR. PAGE: You bet.

DR. FARB: Thanks, Dr. Page. Andrew Farb, FDA.

For the slides that are being presented with the Kaplan-Meier estimates, we should be mindful that when it's mentioned that these are primary efficacy slides or effectiveness, which of course include all strokes, hemorrhagic, ischemic strokes, systemic embolism, and cardiovascular or unexplained death -- and as we get further out, what we really care about with the WATCHMAN device is what's happening with ischemic stroke, right, because we wouldn't expect that that device would have an effect on hemorrhagic stroke, and as we've seen with this patient population, the cardiovascular and unexplained death signal could be quite noisy.

DR. PAGE: Thank you.

Dr. Stein, did you have any further comments on this topic?

DR. STEIN: Just to say that yes, we do again show the primary efficacy endpoint because that was the pre-specified endpoint. And, in our view, it is not the case that the only important endpoint to patients is ischemic stroke. In our view, the endpoint of importance to patients is all stroke irrespective of etiology, all systemic embolism, and mortality.

DR. ZUCKERMAN: Okay, that's well stated, Dr. Stein, but I think as Ms. Neubrander indicated, why are we here today? And one of the questions is how much effectiveness in prevention of ischemic stroke longer term implication on hazard rate is there? And so, as Dr. Page pointed out earlier, I'm going to be asking the Panel to get granular as well as to look at the composite. Dr. Page stated it well before.

Thank you.

DR. PAGE: Thank you.

Now Dr. Cigarroa.

DR. CIGARROA: A question for the Sponsor. Dr. Stein, do you have any information on the renal insufficiency question, and that is, any data in eGFR and associated rates of hemorrhagic complications and/or ischemic events?

DR. STEIN: We do not have data on eGFR in the trial.

DR. CIGARROA: Thank you.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: Just a couple questions while we're allowing the Sponsor to respond. On Slide AA-11, it showed the nice little line. In both the PREVAIL and CAP2, the ischemic stroke rate -- and the next one, please. I'm making it easier. Slide 2, that one. In PREVAIL and CAP2, the ischemic stroke rate was twice as high as it is in PROTECT AF and CAP. Now, first of all, that can't be explained by the CHA_2DS_2-VASc, because the CAP CHA_2DS_2-VASc score was 3.9 and in PREVAIL it was 4.0, and there's a doubling in ischemic rate. And the other thing that would imply is that perhaps the higher the CHA_2DS_2-VASc score, the less likely it is, the device is, to prevent stroke, which would be kind of counterintuitive if you're including the left atrial appendage. So do you all have an idea of why it's twice as high in the more recent studies than the previous ones?

DR. STEIN: Thank you, Dr. Lange. And I think the question that you raise is pertinent, and I think it's best answered on this slide where we see the confidence intervals.

And what you'll note is, out of those four trials, there's one that does diverge, and that's CAP, and the outcomes in CAP are better than what would have been anticipated based on the underlying risk scores. So, again, PROTECT, PREVAIL, and CAP2 line up very nicely with that solid line. CAP point estimates and, in fact, CAP 95% confidence limits are below that line.

Again, one could interpret that as saying that CAP shows the device to be statistically better than an imputed placebo of warfarin. Even for ischemic stroke we've chosen to be conservative and not to say that. Because again, I think, as you look at the totality of data and look at all four of the trials in total, they really do tend to line up with that black line.

DR. LANGE: And then my last question goes back to the FDA slide, which is Slide 62, but it's directed toward you all because I'm just trying to reconcile data, because what I have here is event-free probability, and what you showed are vertical lines with zero points and wide confidence levels, suggesting that there was no increased rate of events after 6 months. So I'm just trying to reconcile those two pieces of data. Slide 62 is labeled "PREVAIL Only," and it shows freedom from ischemic stroke or systemic embolization.

DR. NEUBRANDER: Is this the slide, Dr. Lange?

DR. LANGE: The one just after that. That one.

DR. NEUBRANDER: Oh, that one.

DR. LANGE: And so I'm just trying to reconcile those two pieces of data.

DR. STEIN: So this is now the Kaplan-Meier curve showing freedom from ischemic stroke or systemic embolism in now the PREVAIL-only portion of the PREVAIL trial, and I think that what you see is that there is an ongoing rate of ischemic strokes over time in the

PREVAIL trial. And the graphics just -- maybe it would help if I walk you through it a little bit. So we show not only the point -- the Kaplan-Meier curve, but the 95% -- and I should say the FDA shows -- but this is a slide that we worked interactively with them on. So, if it's all right, I can interpret it and explain. Okay.

And so what you see on that, you know, in addition -- right to the line showing the Kaplan-Meier estimate, the 95% confidence intervals around the line and then the various shading shows the 95% confidence intervals around the performance of the control group, the WATCHMAN group, and then the fact that they overlap is shown by that sort of grayish shading. So you can see that the confidence intervals do overlap between the two trials.

And then again, I think the other point to make here that you see quite graphically is that there's one ischemic stroke event in the entire PREVAIL-only control cohort, a rate that really we would urge you to think about and whether that's actually plausibly going to be duplicated in real-world clinical practice.

DR. LANGE: And while I'm just reading that, does it look like the event rate changes in the device group from 0 to 12 months versus 12 over 24 to 30 months, or is that --

DR. STEIN: Again, the rates obviously always increase with time. It's time-to-first-event analysis, so it always goes down with time. I think, given the small number of patients in the trial, over this follow-up we can't make any robust conclusions about the shape of the parameter of the curve just using the PREVAIL data.

DR. PAGE: Let's leave the slide up. I know Dr. Noonan and Dr. Kandzari and Dr. Kelly have questions, but I'd like Dr. Naftel to comment here.

DR. NAFTEL: I just want a quick little statistics lesson here. It's a natural inclination

to show that the 95% confidence limits must do that. But when we're looking at this and say, when they overlap, the estimates must not be different, that's absolutely incorrect, and I need to make sure you understand that. It is correct at a p level of like 0.01 or 0.001. If you're really in a 0.05 way of thinking, you should be looking at the 70% non-overlapping confidence limits. So I want to make sure everybody is clear on that.

So, in fact, if you -- all of those confidence limits -- divide them in half and then look at where things don't overlap, then you'll conclude that maybe there is something going on, especially when you get to the later time. So anyone that wants to discuss that after the meeting, I do love to talk about it.

(Laughter.)

DR. NAFTEL: Thanks.

DR. STEIN: No. If I may just respond to that, because we agree completely with Dr. Naftel. So I just want to explain. So the reason that we show it this way is we do want to show the 95% confidence limits, particularly around what's in the device arm, because we do think that's very relevant, particularly in terms of understanding the consistency of performance in the device arms of the trials. And so then, when you show two 95% confidence limits, there's necessarily a period of overlap. And so we just needed a way to shade that period of overlap in, just for clarity's sake, on the graph.

I think we have been very up front, and I hope the Panel recognizes that the totality of the data do show that there are more ischemic strokes in these patients if they get treated with WATCHMAN than if they get treated with warfarin. All right, that's not at issue. I think that what is at issue is how that balances in terms of the overall clinical

picture of what happens to these patients: disabling strokes, hemorrhagic strokes, deaths, all stroke, all right? But, again, I can pull back up our meta-analysis, and we are not in a position and we do not want to be in a position to suggest that there's not that difference in ischemic stroke.

DR. PAGE: I believe we've heard that. Thank you very much.

I do want to get on with the questions, because once we're done asking questions of the Sponsor and the FDA, then we need to talk among ourselves and really get to the preliminary discussions before we undertake the questions from the FDA.

So, Dr. Noonan, did you have a question for the Sponsor or the FDA?

DR. NOONAN: Yes, I do. On slides labeled CO-64 and CO-62 in the package given to us, there is a dotted line with a high slope, relative to the solid line, that I assume is some mean curve that fits the data. And that dotted line, is that the imputed analysis of expected stroke rate?

DR. STEIN: I'm going to invite Dr. Reddy up to explain, really, the genesis of both of those lines, the dotted line and the solid line.

DR. REDDY: Yes, this is from -- again, just to remind everyone, this is from the Friberg study, the large 180,000 or so patients in the Swedish AF cohort, and the dotted line represents patients that were not treated; the solid line represents those treated with warfarin. And we could put the dots on there. We just didn't put them on there for clarity, but there's not much divergence from that line.

DR. NOONAN: All right. Now, the event rates in Slide 64 are imputed untreated annual event rates, and then on this, Slide 62, we have events per 100 patient-years. Are

those numbers convertible? Is there some conversion?

DR. STEIN: I think I can answer this. They're not easily -- well, actually, I think that these are annual event rates as opposed to presenting events per 100 patient-years. I think they are convertible. But we actually present, if you will, three different types of imputed placebo analyses here. And so there's this imputed placebo analysis which we did using the Gage data. There's the imputed placebo analysis that we showed in the next slide, where we used the much more contemporary Olesen data. And then also I think, as you've recognized, you can also use that slide with the two lines as another way of doing an imputed placebo analysis.

The reason we did that is I think that we all recognize that one has to be cautious in looking at an imputed analysis as opposed to looking at results for a randomized trial, and in order to get reassurance that these imputed placebo analyses really could provide some guidance to the Panel, we thought that we ought to look at multiple different ways of doing the analysis. And the fact that over all of these different ways of doing the same analysis using different datasets for imputation, that we get relatively similar results gives us a good deal of comfort, and I hope it gives the Panel a good deal of comfort that they can take reassurance from the imputed placebo analysis.

DR. NOONAN: Regarding that, on Slide 64, the imputed untreated annual event rate is different for PROTECT as PREVAIL. Would that then give us two different dotted lines possibly?

DR. STEIN: No. It's a different imputation based on the underlying CHA_2DS_2-VASc score. So it's a higher-risk population in the two, so you get to a somewhat higher imputed

event rate. If we go back to that other -- again, that's of a different data source than we get off that line, but that would be the equivalent of moving up and to the right on that dotted line.

Again, I think, just also in terms of comparison, we've done these in a number of different ways. So one of the tables that you were looking at was in terms of $CHADS_2$ score. This graph is in terms of CHA_2DS_2-VASc score, and the imputation via Olesen is via CHA_2DS_2-VASc score, again reflecting imputation against more contemporary cohorts of patients.

DR. PAGE: Thank you.

Dr. Kandzari, did you have a question?

DR. KANDZARI: Yes, thank you. I have two questions for Dr. Stein.

Number one, I was impressed with the number of statements from our public session regarding the use of this device potentially for patients who were not studied in these trials, that is, patients who are completely not eligible for warfarin anticoagulation. And so it reminded me of asking you about the bleeding rates in this trial. So the major bleeding rates, as I recall, were around the order of 10% to 11% in total; however, about half of them were related to the procedure in the WATCHMAN cohort and about half of them were non-procedure related.

My first question for you is, can you remind us how bleeding was defined and reported? Is this site reported? And were the bleeding definitions or the criteria the same for the procedural aspect as they were for post-procedure?

DR. STEIN: Yes, thank you for the question. I just want to start by emphasizing the Sponsor's point of view. The indication that we are talking about today and the indication

that we are seeking is the one based on our trial design and based on our labeling. It mandates the ability to take warfarin for at least 45 days post-procedure. Patients do need to be eligible for warfarin, and these need to be patients who would be recommended for warfarin therapy.

Now, in terms of the definitions of bleeding, actually major bleeding was adjudicated -- actually site reported, but then adjudicated by the CEC. Major bleeding was a significant adverse event if it led to -- either it was life threatening, led to hospitalization or prolongation of hospitalization, or led to significant disability or death. Now, it's clearly very different types of bleeding that you'd see periprocedurally versus what you might see -- you know, outpatient chronic bleeding, particularly those on warfarin. So it included such things as pericardial effusion with or without tamponade, groin complications -- and those would make up the vast bulk of the bleeds that were seen in the 0 to 7 days versus for the long-term bleeds -- again, I think the things that we're all sort of familiar with in clinical practice: GI bleeds, as you heard, hematoma, epistaxis if it was severe enough to result in hospitalization, major bleeds requiring transfusion, et cetera.

DR. KANDZARI: Okay, but is it fair to say that there weren't, so to speak, standardized criteria then applied? It was more of a site-reported gestalt of a serious bleed or an SAE? Is that fair?

DR. STEIN: So it is fair that it was site reported and then re-adjudicated by the CEC. I think, as we discussed at the last Panel, there was a recommendation that we prospectively develop criteria for bleeding, and we have mechanized that and will implement that in our post-approval study.

DR. KANDZARI: Okay, thank you. And so I'm going to turn to a different direction now for my second question, and that is that I'm coming from the space recently of sham-controlled trials. And I'm not advocating that by any means here, but the purpose in some of these studies is that we're looking for biologic efficacy of a device or a translational mechanistic efficacy of it, and I'm struggling to find that here in this trial for two reasons. Number one, as a first line of evidence, if more than 90% of embolic strokes do come from the atrial appendage, why are we seeing at least a numerical excess, especially late, of ischemic strokes with this technology?

And, secondly, I think we're perhaps in some ways giving a little bit too much credit to the technology for reducing hemorrhagic stroke, inasmuch as it may just be the natural history of repeating historical trials of aspirin versus warfarin anticoagulation for atrial fibrillation, and we're simply seeing a higher rate of hemorrhage with warfarin and we're seeing a lower rate of intracranial hemorrhage with aspirin but a higher rate of ischemic strokes. So even if we took the device out of the equation here, would we not simply be seeing what we've known to occur from predicate clinical trials?

DR. STEIN: Thanks. I want to emphasize that the data show, I would say relatively conclusively, that the mechanism of cardioembolic stroke in these patients is predominantly related to thromboembolism from the left atrial appendage, and that's based most on the fact that we see an equivalent reduction for all stroke, as is achieved with warfarin, when we look at the pooled data, but also that probably the best evidence for this comes from the imputed placebo analysis. And I'll ask Dr. Huber to come up and readdress that point.

DR. HUBER: Thank you. Dr. Huber from Saint Luke's Mid America Heart Institute,

Kansas City.

You know, from a mechanistic perspective, that is a fundamental question that was raised by the FDA, and you are all going to have to think through to determine whether or not the whole idea of left atrial appendage occlusion is legitimate as an alternative to warfarin.

I think I look to this imputed placebo analysis as being very helpful to help me answer that question. The way that I interpret this information is that both WATCHMAN and warfarin, to very similar degrees, not identical degrees, but very similar degrees -- about 75% with WATCHMAN and 83% with warfarin -- reduce the risk of stroke versus nothing versus placebo. And if the mechanism of action was not in play here, I can't really come up with another way of why WATCHMAN reduced the risk of stroke by 73%, other than the fact that it had to have excluded clot coming from the left atrial appendage.

So clearly there are other reasons, in these patients, why they can have ischemic strokes. Remember, 700,000 strokes in the U.S. Only 25% of those are related to atrial fibrillation, so 70 are related to something else. Thirty percent are cryptogenic. So I think there are other things at play here. But this imputed placebo analysis assures me that by closing off the left atrial appendage, it does reduce the risk of ischemic stroke.

DR. KANDZARI: Thank you.

DR. PAGE: Thank you, Dr. Kandzari.

Next, we have Dr. Kelly and then Dr. Patton.

DR. KELLY: Along the same line, I just wanted to comment on Dr. Lange's comment about would the people with higher $CHADS_2$ scores be expected to do better with the

device?

DR. PAGE: Okay, do you have questions for the Sponsor?

DR. KELLY: Yes, I do have a question.

DR. PAGE: Okay, go ahead.

DR. KELLY: So you know what? It can wait because it's more a comment.

DR. PAGE: Yes, we'll have you lead off once we're talking among ourselves.

Dr. Patton.

DR. PATTON: Thank you. Kris Patton.

I have a question for the FDA. Slide 146 in the packet, the FDA summary of benefit-risk. I'm struggling a little bit with how to incorporate the data about the cardiovascular and unexplained death and the overall death. And you caution us in this slide to remember that the mortality difference is driven by reduction in fatal hemorrhagic strokes, but clinical circumstances should be considered when attributing this benefit to the device. And I realize that's because of, as you put it, the noisy signal of the subdural hemorrhages. But I'm wondering if you could elaborate a little bit more, knowing that patients on warfarin probably have a worse outcome from subdural hemorrhages when they hit their head.

DR. FARB: Thank you. Andy Farb from FDA.

A couple of points. So the noisy signal really refers to those non-stroke related events, and that is the other underlying cardiovascular comorbidities as well as the acute MI and heart failure types of deaths, which we really can't attribute to either the device or the warfarin.

And you make a very good point about, certainly, if patients are on anticoagulation,

the seriousness of any type of cranial bleed may be increased versus not being on antithrombotic therapy. But, in particular, you know, a good percentage of those patients who are also on dual therapy with aspirin -- and remember, with the device early on, if they occurred, those patients are obligated to take both warfarin and aspirin, in a patient who otherwise would probably be just on warfarin alone for their atrial fibrillation.

So it is a very complicated kind of analysis or consideration, but the idea really is that bleeding in your head is a bad thing. It can lead to serious morbidity and mortality. And whether it's a hemorrhagic stroke or a fall and a subdural hematoma or a spontaneous subdural hematoma, the risks increase -- or seriousness -- by the compounding of antithrombotic therapy.

DR. PATTON: Thank you.

DR. PAGE: Thank you.

Dr. Lange and then Dr. Brinker. And I will ask you to just pose specific questions to the Sponsor -- and Dr. Brindis -- the Sponsor or FDA, because I was hoping we could get started on our deliberation before the 3:15 break.

Dr. Lange.

DR. LANGE: Just a specific question. Either the Sponsor or the FDA. I'm still confused by the hemorrhagic strokes, in that some of them are subdural, some are intracerebral. And so can either of you provide that data for me for PROTECT? PREVAIL is not an issue because there's just two on either side. So that's not statistically significant.

DR. STEIN: Yes, I can show that to you for both trials at once, and I can remind you, just for clarity's sake again, of the pre-specified definitions that were used by the CEC in

making their adjudication.

So, to begin, in PROTECT AF, hemorrhagic stroke was defined as the sudden onset of a focal neurologic deficit with CT or MRI evidence of tissue loss with evidence of blood vessel hemorrhage, and a subdural hematoma, therefore, that was limited to the subdural compartment was not adjudicated as a stroke. Using those definitions, only three of the hemorrhagic strokes in PROTECT were subdural hematomas. In every one of those three, there was evidence of intraparenchymal bleeding as well as the subdural hematoma. In PREVAIL, the definition was very slightly different. It would include a subdural hematoma with a focal neurologic deficit as a hemorrhagic stroke. There was only one of those, and it was in a WATCHMAN patient.

And I would also again -- because I think, just for clarity's sake, there was one patient in PROTECT who had a hemorrhagic stroke adjudicated by the CEC, who did not have any imaging performed -- and both we and FDA have discussed this case already today. That was a patient who expired in the emergency room after presenting with focal neurologic symptoms but before the imaging could be performed. That eventuality just had not been considered in making these definitions. The CEC used their latitude to call it a hemorrhagic stroke. But even if it hadn't been an adjudicated hemorrhagic stroke, nevertheless it has to be adjudicated as a primary endpoint event.

DR. PAGE: Thank you.

Dr. Brinker.

DR. BRINKER: Dr. Farb, I got the feeling that you didn't quite buy into the analysis for imputed rates of ischemic stroke in patients who were untreated, and this is an

important issue to me because if a person really couldn't take any anticoagulant, the question is, is the WATCHMAN better than nothing? And I need to have a little bit more explanation by you, whether in fact you're just trying to open our eyes to other possibilities or whether you really doubt that this analysis reflects truth.

DR. FARB: Well, in fact, as has been mentioned, Dr. Brinker, we did ask for this analysis because, knowing that it would be a question on the table and for discussion -- and the Sponsor complied and performed it and it does give some information, but it comes with a great deal of caveats as well. And remember, we have to -- when we're talking about approving a device, that indication for use has to be based on the data we have available, based on the clinical trial information that have been presented to us, so that we don't have a trial here of the device versus no therapy or ineffective therapy.

So I think it is an interesting analysis. We are open to hear from the Panel what they think of it. We've pointed out our concerns with going too far with that analysis because it's mixing and matching different trials and just basing prospective event rates on something as important, but not everything, just the $CHADS_2$ or CHA_2DS_2-VASc scores.

DR. BRINKER: Thanks. I'm caught on this because I think if we knew for sure the results of a study, that would never be done, which is a randomized controlled study of no therapy versus the WATCHMAN. I don't think it would be done.

DR. FARB: I'm not sure. Well, I mean that's another item for discussion about equipoise. But, again, this device is supposed to prevent ischemic stroke by preventing embolization from the left atrial appendage. Has that case been made? And that's, I think, the critical question on the table. And does it do it well enough to offset any risk associated

with the device?

DR. BRINKER: Thank you.

DR. PAGE: Thank you, Dr. Brinker.

And I will mention that, before we close this question and answer segment, we will allow the last word to go the Sponsor.

Dr. Brindis.

DR. BRINDIS: Could I have Sponsor Slide 81? This is on the post-approval study. So one of the key questions, of course, has been the debate about whether there's been a divergence related to late findings in terms of ischemic stroke. And I know that you have substantially enhanced your idea of a post-approval study since our last Panel, and with this question on the table, I would assume that if the Panel ends up recommending to the FDA for approval and the FDA does approve the device, the post-approval study is going to have even more importance.

It also builds on a comment that Dr. Kandzari made and Dr. Brinker has made. And I'm going to allow you to have open discussion on this. Here you are suggesting we have 1,000 new patients. It would be that we have data for 5 years. We would do some prospective analysis and look at pre-specified endpoints. But one of the questions is, is this also an opportunity -- I would always want more patients, of course, but is this an opportunity to look at registries that we have out there -- like the PINNACLE registry from the NCDR, which has now quite a few patients related to atrial fibrillation, both who are on anticoagulants and also 50% who are not on anticoagulants -- as a way of reassuring the Panel and the FDA related to their concern of this signal of divergence?

DR. STEIN: Thank you, Dr. Brindis. I'm going to answer your question about the particular post-approval study and registries. And in thinking about potential post-approval studies, I can also, I think, give some more clarity to the last question that was asked regarding the contraindicated -- pure contraindicated population.

So, to begin with, we absolutely would appreciate your thoughtful consideration and guidance on how best to construct a post-approval study that would help validate safety and real-world outcomes of the device. Could that be accomplished through a large-scale registry? We would actually welcome your advice on that. I think doing this through a comprehensive large-scale registry could be quite attractive, as long as that would be constructed in a manner that's not unduly burdensome to the Sponsor and that's not unduly burdensome to patients and implanting physicians, and as long as it would meet all of the needs of the FDA in lieu of this particular study that we've proposed.

As we move from that and think about other studies that could be done post-approval, I think -- first off, you know, just again and just clarifying, as we think about the imputed placebo analysis and the patients, please, again I do want the Panel to bear in mind that the indication that we are seeking today in accordance with our labeling requires patients to be able to take warfarin for at least 45 days. And so as you think through that imputed placebo analysis, that's a benefit -- 60%, 70%, 80% versus taking nothing -- as long as you're able to take warfarin with the device for the 45 days. Okay, it is not a comparison that would involve patients getting the device but not getting any periprocedural drug therapy. That is, on the other hand, very clearly a group of very great interest to practitioners.

We have run a registry study that was run in Europe, called ASAP, that provides early evidence of the feasibility of that approach. That's not what was under consideration today, but we have had some discussions with FDA that if the device should be approved for this indication, it is our intention to submit an IDE to the Agency for a multicenter randomized trial in the truly completely contraindicated population, that is, the population that can't even take warfarin for 45 days. But, again, I do want to emphasize that that is not the intended use that we're discussing today.

DR. PAGE: Great, thank you.

Yes, sir.

DR. FARB: Just a quick comment. FDA would be highly interested in a study that would look at patients who are unsuitable for anticoagulation for this type of device.

DR. PAGE: That's very helpful.

We're getting a little bit ahead of ourselves. If I'm not seeing any other questions from the Panel and Dr. Stein, you've had a chance to respond, then I'm going to now bring us into the portion of our meeting where we, as a Panel, deliberate among ourselves. I want to open the floor to the experts around the table to begin deliberating on any issues that you may have with the data you have heard today, either this morning in the Panel presentations, the discussions with the FDA and Sponsor, or the material that you've read in your Panel packets.

And, Dr. Kelly, you've been very patient. Why don't you share with us the concern you were going to raise earlier?

DR. KELLY: Well, I just wanted to explore a little bit more about the concept of

non-cardioembolic strokes, because although it's true that 90% of cardioembolic strokes are caused by left atrial appendage clot, that's not 90% of strokes all told.

And then going back to Dr. Lange's comment about well, why wouldn't the people with the higher $CHADS_2$ scores get even more benefit from the WATCHMAN, I think we have to consider that those people might have more reasons to have other strokes. They're older. They may very well be more likely to have aortic plaque. They might have more carotid disease. So I think we can't forget that maybe part of what's going on here is that maybe the WATCHMAN, to a great extent, is preventing left atrial appendage strokes, but then do these people have other reasons? And I think that probably they do.

The other thing -- I don't know if there are any data, but I've looked and can't find -- but there are some small reports that people with WATCHMAN, they may have leaks initially and then they close. But there are some small reports saying that over time they can develop new channels that cause flow between the appendage and the main left atrium and that those channels can enlarge. So I think the fact that we may be seeing more strokes later on might relate to that.

DR. PAGE: Thank you.

At this point I'll take the Chair's prerogative to ask Dr. Naftel to help frame the discussion with regard to the statistics we've been hearing about today. And one question up front. Since I was not at the last Panel, the meta-analysis was undertaken by the Sponsor as an instruction from the Panel, I believe, not from FDA, in terms of being one analysis. And we've heard a lot about those pooled data. Were you the person who thought a meta-analysis would be valuable? And do you think that it does inform our

conversation today, or do you have problems with that? And then after that, if you'd help us frame the statistical back-and-forth we've been hearing.

DR. NAFTEL: I'm not sure if I'm the one that asked for the meta-analysis or not, but I thought it was very useful. It's interesting to me that we had to label it -- you had to label it "Patient-Level Meta-Analysis," because meta-analysis, by definition, is not patient-level. It's looking at effect sizes in different studies and combining them. So you've come up with a new term, so you need to make sure, because that's a contradiction. Patient-level meta-analysis doesn't exist. But combining the results at a patient level, that totally exists, and that's what was done, and I think it's quite useful, and it's sort of a poor man's Bayesian analysis. You're combining the information from two studies and, of course, it gives weight according to the number of subjects in each study. But I thought it was quite useful for me to see that.

And then if I may go to your first question of -- so I know we're not going to talk to FDA for a second, but if I could see one of their slides. Could we go to Slide 41? Because I think it's the slide about why we are here. Yeah, let's see if we can do that.

DR. PAGE: And, again, I'll remind the Sponsor and the FDA, we will not be calling on you, unless we call on you.

(Laughter.)

DR. NAFTEL: And I'm not actually calling on you. I'm just asking for the slide.

DR. PAGE: Exactly. Thank you.

DR. NAFTEL: Yeah. So while she's getting that together -- so obviously I believe -- oh, that's really nice. Okay. So can you go to -- it's Slide 41 in the handout, so it might be

around 44 or 45. It's the one that shows the ischemic rates before and -- yeah, that's not quite it. That's almost it. This is PREVAIL-only from January 2013 to June -- no. No.

UNIDENTIFIED SPEAKER: Slide 41?

DR. NAFTEL: It was 41 in my packet. It says PREVAIL-only, and it's the ischemic stroke rate per 100 patient-years.

DR. PAGE: So, if it's 41 in our packet, it will probably be somewhere around 45 there.

DR. NAFTEL: Yes. It's a bar chart. There it is. Okay. So let's look at that for a second, and let me see if I have the point of why we're here. So, in the earlier data that we reviewed last year for the ischemic strokes in the WATCHMAN group, there were five strokes, and in the control, the warfarin group, there was one stroke. And now we're here because there's an additional eight ischemic strokes, and I think that's the main reason we're here.

So the interesting thing to me is if you took that event rate in the early time period and continued it with the extra follow-up, you would have another 6 patients or a total of 11 patients if the rate that we all approved -- if that rate stayed the same, we'd go from 5 patients to 11 patients. And, in fact, we've gone from 5 to 13. So, in my mind we're here -- for all of the fancy statistics and fancy analyses, we're here because of two excess events. So we have p-values to the fourth decimal point, which I would never do. We have rates to the fourth decimal point, and it implies a precision that isn't there. I think we're here because of two patients. And then if you look at the control group, they had one event early and now they still only have one event. The follow-up time is roughly double, so the

rate is cut in half. So, if we just had one more event in the control group, as we expected, if we had two less in the WATCHMAN group, I think we wouldn't be here. So, to me this is the most informative slide of the whole thing, and it makes me not -- if you'll forgive me for a conclusion, it makes me not very upset over those eight patients.

DR. PAGE: Thank you, Dr. Naftel. You were the statistician on the Panel in December; is that correct? And I looked at the DVDs and I know you were not the dissenting vote. Very often it is the statistician who points out that the stats didn't work. And in that vote you were considering three endpoints. Aside from the safety, you had one met and one didn't, and now you have two that don't meet. So, if we got it right before, you're saying we've got it right now, but you think we got it right before.

DR. NAFTEL: I actually do. And I totally believe in the whole method of analyses. I think the analyses by both parties are quite good, and if you just relax, they're easy to understand.

(Laughter.)

DR. NAFTEL: But you get back really to the classical 0.05 significance level. You know, Fisher came up with that and only because someone just bugged the hell out of him and said give me something. But to a statistician and to a researcher, 0.04, 0.06 -- you know, it's all the same. Now, we've crossed the line a fair bit into the not good area, but I'm just -- personally, I'm not bothered.

Just one more comment. We need to change our words. When you say mortality favors one group, what on earth does that mean? Does that mean death is better in one group than the other? So both sides need to work on your language because -- I don't

know. If you said survival favors, I get it. But mortality, that's a double negative, and I'm confused, so don't do that.

DR. PAGE: A point well made. We have a few minutes to talk among ourselves. Are there any just general comments from the Panel?

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

It's actually a question for Dr. Naftel. I found myself, during the discussion -- and Dr. Zuckerman seemed to read my mind at one point -- being underwhelmed by the use of patient-years because of the short-term of the study. It seems to me patient-years is a more important thing when you're dealing with long term. So I'd like for you to tell me if I'm right or wrong or what.

DR. NAFTEL: So that's a great question. The FDA, when they first started really being serious about analyses with heart valves, really got into patient-years and linearized rates. So that has stuck around for a long time, and it's been a good thing. The reason you're uneasy is really what Dr. Zuckerman was referring, is if that linearized rate is based on short-term follow-up, you're uneasy because you're thinking maybe the rate is higher. And certainly for many things, procedural bleeding and all, they are higher. If you can make the assumption and prove it somehow, that these rates are the same whatever the event is during the first 30 days or 10 years later -- for a month -- if you think they're the same, then it's okay to look at these rates. But I think you should be nervous and you should look at the rates that we were seeing by time intervals and you'll feel better or worse. And there are formal statistical tests that I think weren't incorporated. And there are better methods,

by the way. The Nelson cumulative event method is the right way, in my opinion, to show rates across time and accumulating them. And if it's linear, you have a constant hazard. If it's not, you don't. But I'd say you're right to be uneasy.

MS. CHAUHAN: May I follow up with one other?

DR. PAGE: Yes, ma'am.

MS. CHAUHAN: This is more just for anyone who wants to tell me. When you were talking about the risk of aspirin usage and that you weren't sure if there was much difference between the device and aspirin, if I understood, with ischemic strokes, the group I started to think about that might be identified as a subset that this is important to are people with renal failure for whom aspirin is a real problem, where they have also renal failure in addition to the heart problems. I'm wondering again, is that true or am I off base?

DR. PAGE: Does anybody want to respond to that specific question? Then I really want to get to Dr. Patton.

Dr. Cigarroa.

DR. CIGARROA: So it is clear that renal failure is both -- provides both an excess risk for cardiovascular events -- and so the probability of infarcts or stroke -- and secondarily is also an excess risk for bleeding with any of our therapies, whether it is something like aspirin or something like warfarin.

DR. PAGE: Thanks, Dr. Cigarroa.

Dr. Patton.

DR. PATTON: Kris Patton.

I want to piggyback on Dr. Yuh's question and ask Dr. Naftel's opinion. You know,

Dr. Farb kind of put this together really nicely in terms of this issue of whether the WATCHMAN device prevents ischemic stroke well enough, and I think that's what we're all really struggling with. And I'm wondering -- I do not have a good sense in terms of structures of non-inferiority trials, if the success criterion of 97.5% is high, middling, low, accurate. What's your thinking?

DR. NAFTEL: I just don't know what to say.

(Laughter.)

DR. ZUCKERMAN: Okay. So Dr. Naftel --

DR. PATTON: I apologize for putting you on the spot.

DR. ZUCKERMAN: Excuse me, could I just state -- Dr. Patton, you're asking the right question, but Dr. Naftel can help guide you to look at the parameter which is most of interest in looking at non-inferiority trials. The 97.5 criterion is a tough criterion. But what's really important, as a group of clinicians, is to ask yourself what the margin is for the first primary effectiveness endpoint and the second one. That's why in PROTECT AF the risk ratio was changed from less than 2.0 to less than 1.75 in PREVAIL. And Dr. Yuh has also questioned the 0.0275 rate difference. So those are the parameters which are of more importance. You can always show something statistically if you have enough numbers or if you're lucky enough, but does it mean anything clinically?

DR. PAGE: And what I was going to pin down Dr. Naftel on is I think what Kris was asking is are you -- in terms of the endpoint, the endpoint was missed and you say you're not bothered by that. And I hear that, but was the endpoint right? Did we set the bar high or did we set the bar low in terms of demonstrating non-inferiority? Do you have an

opinion on that?

DR. NAFTEL: I think those figures that you showed with the 1,000 patients and how many died and how many had events, that would be a great thing to have for this discussion so that we could say here's what would be acceptable with warfarin, you know, with all the little dots, and here's what it would be for the control group. And then we get to flip the question back to you. You know, at what point do you get unhappy when those diverge? And it becomes more of a clinical or even a public health question -- you know, what's okay?

I think it was a pretty strict and difficult bar to handle. I would love to literally put all of the results, just like you guys did, in those per 1,000 patients. It does miss one thing; it misses confidence intervals. You know, given some time we could lay that all out, and then you could tell me, oh, 15 patients out of 1,000 versus 10, I'm not concerned. But when it gets too big, I get very concerned.

DR. ZUCKERMAN: Okay, but Dr. Naftel, that's a good way forward, but you seem to be looking to your right today. I'm wondering if you could look to your left also, to Dr. Furie, to ask her about the estimates, that they're using the data that they've utilized for this risk-benefit framework. Because all of this is imputed, it's very dependent on which articles you pick and how you compare different trials which are not apples with apples necessarily.

So, Dr. Furie, can you help us out from this quandary?

DR. FURIE: Yes. And I have to agree with that sentiment. You know, we saw different graphs that selected out different comparator trials to demonstrate a benefit over

placebo effect, but the rate is going to vary. For instance, the community rates of stroke, if you're not actively managing warfarin in a trial, are going to be quite different than those in an active trial where there's much closer management to the INR, including patients who have a previous history of stroke or TIA is obviously going to impact the risk of recurrent events. And so I do think it's a little misleading, necessarily, to look at all of those strokes pooled out of one or more published studies and then compare it to the experience in these clinical trials.

DR. PAGE: So may I ask you, does that tilt you more toward being convinced that this is a benefit or away from that opinion?

DR. FURIE: So, you know, I see two different analyses that have failed to prove non-inferiority to warfarin therapy, and despite the numbers being small, the number of patients who will ultimately potentially receive this intervention, I think, is quite large. We've heard about the burden of atrial fibrillation in this country, and these are patients with atrial fibrillation who are candidates for anticoagulation. So that's almost everybody, if you think about it. It's patients who choose, or their doctors offer them, the opportunity to have a device rather than be on chronic medical management. And so I do worry that even though the numbers are small, we're not seeing a benefit and we've not demonstrated non-inferiority to the standard treatment.

DR. PAGE: Thank you.

I do want to do a time check. We're now at the time when we should be taking a break, but I'd like to go a few more minutes and have a shorter break. At 3:30 we need to start addressing the questions. So I'll ask for comments that will inform the discussion, as

much as anything, once we get into the questions and we'll be going through them individually.

Dr. Cigarroa and then Dr. Lange.

DR. CIGARROA: So, just a couple of points. Number one, when we say device, it is device coupled with pharmacologic therapy. So it is WATCHMAN and for a period warfarin and aspirin, and for a period aspirin and clopidogrel, and then aspirin indefinitely. So the ischemic event rates that we're seeing are despite device coupled with antiplatelet therapy.

The second is when one looks at the composite endpoint, we see a divergence of maybe excess ischemic event rates in the WATCHMAN plus an antiplatelet therapy long term versus an increase in hemorrhagic event rates through WATCHMAN plus antiplatelet group and the control arm. And we have to think about the patient demographics and some inherent biases in the real world and clinical practice, and that is that despite the data that we know about as cardiologists and neurologists, there is a frequent number of patients who are on both warfarin and antiplatelet therapy, and part of this composite efficacy endpoint is being driven by the excess hemorrhagic rates in the control arm.

And so, as we go through these discussions, I just want to make sure we take time to talk about what the signal is from the device and what the signal is from antithrombotic therapy and antiplatelet therapy.

DR. PAGE: Great, thank you.

Actually Dr. Kandzari was ahead of Dr. Lange.

Dr. Kandzari.

DR. KANDZARI: All right, thank you. Can we pull up the Sponsor Slide 70, please?

And while that's coming up, really I'm going to look to my left, to Dr. Naftel here, for further clarity on some of his comments. I think if I understood Dr. Furie right -- and I don't want to speak for her, but it felt like we had not demonstrated non-inferiority and I'm still struggling with my comments for the Sponsor, to Dr. Naftel, because you kind of gave me this sense of reassurance that we're here for two patients and two patients only and that there were none in the control group. And I think, just as an aside, that's a hazard any time we do 2:1 randomized trials. While it amplifies our safety signal, we can at the same time have a small control group whose predicted outcome may be substantially off from what we might otherwise have anticipated.

But, Dr. Naftel, if you look at this slide here, too, the reduction in hemorrhagic stroke in the absence of anticoagulation seems intuitive, but we're seeing a trajectory in the opposite direction with ischemic stroke. And, again, with the comments about, well, this is just two people compared with December 2013 -- help frame that for us.

DR. NAFTEL: So, just a quick thing about this slide. For every p-value there's a hypothesis, so the hypothesis says that there's no difference. So those are superiority p-values. You could think of them that way, just by the way.

The other thing that's fascinating to me, both FDA and you just said -- and others have said it -- that hemorrhagic stroke isn't very important in some sense because you expected that.

DR. KANDZARI: I think it's important.

DR. NAFTEL: I'm sorry. But because it's expected, it's almost like we're not paying attention to it. So I think it's great that it's happening the way you expect and then -- so

that's one thing and it's a good thing -- it's way to the left. The ischemic stroke is to the right, and you'll notice that the confidence on it touches right on 1 and the p-value is 0.05. So, okay, it didn't make it. The all stroke is just right in the middle where there's no difference. So I don't know. And I don't mean to say the whole thing is driven by just two patients, but this almost deserves one of those cool sensitivity analyses where let's move one or two patients from one side to the other and just see how sensitive this whole figure is to just a few events. These are fortunately rare events, and it's hard to analyze them properly.

DR. KANDZARI: I say this only because it goes back to my earlier comments that this may simply be the natural history of a comparison of aspirin versus warfarin anticoagulation. And from what I've heard from the other presentations is that the proof of concept here is really based on an imputed placebo, and it's an imputed population that, as I understand it, was placebo and not even aspirin therapy, as these patients with the WATCHMAN device were treated with aspirin.

DR. PAGE: Dr. Furie had a brief clarifying comment, and then I'm going to take a break and then have you start after the break, Dr. Lange.

Dr. Furie.

DR. FURIE: Yes. I don't want to minimize the importance of intracerebral hemorrhage, but it is concerning that many of those events occurred in the setting of combination warfarin/antiplatelet therapy and not all of them are intracerebral hemorrhage. We heard that as many as four were actually subdural hematomas and were not hemorrhagic stroke per se. And so, even though the graph is very dramatic, because

those data are coming from a study where ICH wasn't rigorously adjudicated, I suppose, or at least the definitions were a bit looser, and because of that unusual dual antithrombotic therapy, I think it's hard to then interpret that in terms of a pure warfarin effect.

DR. PAGE: Great, thank you.

We are now going to take a 10-minute break. Panel members, please do not discuss the meeting topic during the break among yourselves or with any member of the audience. We will resume at 3:35.

(Off the record.)

(On the record.)

DR. PAGE: Okay, I will now call us back to order. Before we focus on the discussion regarding the FDA questions, are there any further questions or comments from the Panel?

(No response.)

DR. PAGE: Dr. Lange had a question or a comment, but he may have just missed his opportunity and we'll bring that --

(Laughter.)

DR. PAGE: He'll be able to speak as we go into the questions.

Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations we've heard, and the expertise around the table.

With this said, I would like to ask each Panel member to identify him or herself each time he or she speaks to facilitate transcription. We'll do our best with that.

Dr. Lange, in your absence, I mentioned that I had promised to call on you for any comments before we undertake the questions. Having seen the video of the last panel, I recognized that you were the dissenting vote. Do you have any comments before we undertake the questions?

DR. LANGE: Well, I wish I wasn't so recognizable.

(Laughter.)

DR. LANGE: But I was. And here was the reason. There were a number of difficulties with the PROTECT AF trial that warranted the FDA, with the Sponsor's agreement, to embark upon a second trial with agreement to do a Bayesian analysis, statistical analysis where the PROTECT AF would inform the second trial. And then after only 28% of the people had reached the endpoint, the Sponsor brought this for approval. And I wasn't convinced at that point. You couldn't have enough data. And now we have, I think we have, enough data and the data look very similar. And I'm not quibbling about one or two patients. Like Dr. Naftel says, I can lose a couple of those in the hospital and not know where they're at.

But if you look at the combined stroke rate, at the December 2013 -- it was 2.7% versus 0.7%. And now, with all the data, it's 2.7 versus 1%. It's almost a two and a half or threefold difference. If this was a question of different pharmacologic agents and one had a stroke rate of 1% versus 2.7% and you were trying to convince me that 2.7 was non-inferior, I'd have a hard time. So I think what the data tell me is not that there's a couple more patients, but the data now, with more robust information about -- well, I think it's a much better trial. Give me the same information as back in 2013 and it's no more reassuring, I

guess, is what I'll put --

DR. PAGE: Just for clarity, when you say stroke rate, were you referring specifically to the embolic events?

DR. LANGE: No, sir. That's total stroke rate. That's total -- it's 2.7% versus 0.7. That's ischemic and hemorrhagic. And then now, 2.7 versus 1%. For both, total.

DR. PAGE: Do you want to pull up the slide that reinforces that statement?

DR. LANGE: Sure. In fact -- we want to go to -- and I'm looking at the FDA, the Executive Summary, Table 1, that shows the rates. And I don't know if you have that, if you can pull that up.

DR. NEUBRANDER: Just give me one minute.

DR. PAGE: Dr. Neubrander, you'll pull that up for us?

DR. NEUBRANDER: Yes.

DR. PAGE: Great.

DR. LANGE: It's a Sponsor and FDA analysis. So this is stroke and systemic embolization, total stroke and systemic embolization.

DR. PAGE: And I appreciate the Panel's indulgence, but I do want to have the data in front of us to allow us to continue our discussion.

(Pause.)

DR. PAGE: Not to put you on the spot, Dr. Neubrander. Should we move on or do you have it there?

DR. NEUBRANDER: I almost got it.

DR. PAGE: Okay. I guess I was putting you on the spot.

DR. NEUBRANDER: Okay, here's the Executive Summary. Page 12.

DR. LANGE: On the left, it's -- the top part is January 2013, the bottom part is June 2014. The top, the first three rows are stroke: ischemic, hemorrhage, and systemic embolization. Add those up. So there are seven in the WATCHMAN group in January versus one in control. If you go down to June 2014, that's 16 versus 3. And so the rates are essentially similar.

DR. PAGE: And, again, those are absolute numbers you're pointing out.

DR. LANGE: Yes.

DR. PAGE: And we need to keep in mind the 2:1 ratio.

DR. LANGE: Well, the rates are in -- up one, 2.7 versus 0.7, and below, 2.7 versus 1, if you use a percentage rather than an absolute number. So you're absolutely right, Dr. Page.

DR. PAGE: Okay, thank you.

Any other comments from the Panel before we go into reading the questions?

(No response.)

DR. PAGE: Dr. Neubrander, I will now ask you to read the questions. And we'll take them one at a time.

DR. NEUBRANDER: Thank you, Dr. Page.

Question 1: The WATCHMAN device is a locally targeted intervention that is intended to reduce the risk of ischemic stroke and systemic embolism by preventing the embolization of thrombi formed in the left atrial appendage. The rates of ischemic stroke and systemic embolism favored the Control group in both the PROTECT AF and PREVAIL-

only updated datasets. In addition, for the second primary endpoint in PREVAIL, non-inferiority was not met based on the updated June 2014 dataset.

Please comment on the clinical significance of the results from PROTECT AF and PREVAIL, and discuss whether the WATCHMAN device is sufficiently comparable to warfarin in reducing the risk of ischemic stroke in patients with non-valvular atrial fibrillation.

DR. PAGE: And, again, we're taking these one at a time. I'm interested in panelists' perspective on this, and I look to the Panel for whoever would like to comment.

Dr. Slotwiner.

DR. SLOTWINER: I've been quiet.

Well, you know, I was listening to Dr. Naftel's interpretation of those three patients, interestingly, from a statistical perspective. But I think, from a clinical perspective, what's been so concerning compared to the last panel is that this really makes us, I think, as clinicians, have to question whether we can recommend this as equivalent to warfarin. I think there's a clear signal that there are other thrombi, other sources, other than the left atrial appendage, and it is at this point hard to ignore that. So I am concerned.

DR. ZUCKERMAN: Excuse me, Dr. Slotwiner. I'm sorry to interrupt. It doesn't look like everyone is looking at the question pack where there are additional figures and tables, and when you identify your comments, for example, Dr. Slotwiner, can you just let the Panel members know which figure you're looking at? Because I think you're specifically referring to a figure.

DR. SLOTWINER: Yeah, I was referring to the figure that Dr. Naftel had referred to, which is not one of the ones here, but it could be, I think, Table 1 or -- I think we've looked

at this figure quite a bit. So I think there is a clear signal, and the question will be whether it's equivalent to warfarin or better than placebo, but I think there is a concern.

DR. PAGE: Thank you, Dr. Slotwiner.

Dr. Yuh and then Dr. Lange.

DR. YUH: You know, this device very well may be inferior to Coumadin, but really it's not surprising because mechanistically, intuitively, it should be inferior because Coumadin theoretically treats a broader etiology panel for stroke than this device. This device is not purported to prevent strokes that do not originate from the left atrial appendage, and that's okay with me. And the reason why is, that from a surgical perspective, there is somewhat of an analogous situation. For example, in a patient that ranges anywhere from 55 to 65 years old, when you're discussing valve replacement therapies, there are two options: mechanical versus bioprosthetic. And from a durability perspective, the bioprosthetic is clearly inferior; I don't think anybody would disagree to that. There is certainly a much higher rate of structural valvular deterioration.

But patients have that choice to pick it, even though they know, most likely, that they may need another relatively high-risk reoperation to replace that valve when that valve deteriorates. But they do that knowing full well why, and that's because they don't want to take Coumadin. And we accept that. And I deal with that on a weekly basis, when patients try to decide what type of valve prosthetic to select.

And I think this is somewhat -- it's not exactly in parallel, but it has all the same features in terms of decision making and the rationale for choosing a device like this over Coumadin when the patient has an informed decision to make and can make that informed

decision based on the data that we've seen here. I think the totality of the data argues in favor of that choice, and that's where, I think, clinical context -- the way I see it, the way I frame it, and the way I look at it.

DR. PAGE: I appreciate your expanding to the totality of the data. I will ask for the Panel to -- because we will be discussing that exactly, Dr. Yuh. I will ask for the Panel to focus on specifically this question, as posed, regarding ischemic stroke in these patients.

Dr. Lange and then Dr. Cigarroa.

DR. LANGE: I would almost want to cut this part, this answer to this question short because in fairness -- and even the Sponsor admitted that it doesn't decrease ischemic stroke rate. And I applaud them for being honest about the data. The data doesn't suggest that it does reduce, at least, the ischemic stroke rate. Not talking about totality, but the ischemic stroke rate.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: So I concur with the Sponsor and Dr. Lange here. The question is quite specific, "sufficiently comparable to warfarin in reducing the risk of ischemic stroke," and the data does not tell us that it is.

MR. THURAMALLA: Just a question to Dr. Lange.

DR. PAGE: Mr. Thuramalla. Yes, sir.

MR. THURAMALLA: Question to Dr. Lange. The Slide No. 44 from the Sponsor, that the PROTECT AF disabling stroke favors WATCHMAN. So does the disabling versus non-disabling stroke analysis play into this equation?

DR. PAGE: Dr. Lange, I'll look to respond, but I also might ask one of our

neurologically more-oriented physicians might comment, as well.

DR. LANGE: He was going to say the one who's not neurologically impaired. That would be me.

(Laughter.)

DR. LANGE: But I think our neurologist Panel member really described it well. I'll let her do the same again.

DR. PAGE: Dr. Furie.

DR. FURIE: So looking at disabling versus non-disabling stroke is important in determining how significant the events are. The definition for disabling employed here is very unconventional, though. The typical definition for disabling stroke would be a modified Rankin score greater than 2, which means you can't ambulate independently, and we usually judge that at 90 days after the event to allow for some natural recovery.

What we've been looking at is the definition of disability, which is a change in Rankin of two points, which I asked for some clarification because that could take you from a 0 to 2. A 0 is no symptoms at all; a 2 is some symptoms but able to go about activities of daily living independently. So that really doesn't, at least in the stroke world, meet the threshold for disability.

In addition to what I was told, was that going from a 4, which is moderate to severe disability, to a 6, which is death, would also meet the definition here for having a disabling stroke. But going from disabled to death is not necessarily related at all to the stroke symptoms. Oftentimes those are related to medical factors or to withdrawal of care. So again, the way we're getting this information makes it hard to really draw that clear

distinction between disabled, meaning unable to do activities independently, versus independent, in the 0 to 2 range.

MR. THURAMALLA: Thank you.

DR. PAGE: So I'm looking around the table to see if anybody has any further amplification or contrary perspectives or otherwise. Seeing none, Dr. Zuckerman, with regard to Question 1, I believe the Panel is in consensus, if not unanimity, with the Sponsor, who acknowledges that the WATCHMAN device is not necessarily comparable or equivalent to warfarin for this narrow question asked, and that is ischemic stroke in patients with non-valvular A-fib. The issue of how disabling a stroke might be, while this is thought-provoking, I'm not sure that the Panel is necessarily parsing out one stroke versus another but does acknowledge that the embolic stroke rate appears to not have a benefit with the WATCHMAN device.

Does this meet your needs, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, but I have two additional questions based on that good summary.

Dr. Yuh, now that you've heard a good panel discussion, do you agree with the majority here, or are you still comfortable with presenting this device to a patient knowing the difference in ischemic stroke rates?

DR. YUH: I'm comfortable in the sense that the wording of the question, "sufficiently comparable," to me doesn't mean equivalent. Is it close enough to be a valid alternative? And that's why I brought in the valve kind of analogy. There are other examples in medicine where there are other options that are not as, perhaps, potent as another but are still

acceptable, given side effects or other consequences of the ideal therapy. So I think, in my interpretation of the question, sufficiently comparable, that I think it is, in the way I'm framing the question or interpreting the question.

DR. ZUCKERMAN: That's fine. I think that was the spirit of the question.

So is there anyone else who agrees with Dr. Yuh?

DR. PAGE: Dr. Zuckerman, I guess I'm unclear in what was the spirit of the question. We have roll-up questions coming, and it seems to me that I'm hearing from the Panel -- and I guess, Dr. Yuh, maybe I misinterpreted. I thought you were acknowledging that for this specific issue, there are more embolic strokes with the WATCHMAN than otherwise, but in the totality of the data, you were going on to the next questions at hand. But in terms of this narrow question -- I thought it was a narrow question -- that I thought I heard unanimity, including the Sponsor, that there was a signal for increased embolic or certainly no strong data for equivalence in terms of the WATCHMAN device to warfarin.

Did I interpret you correctly, Dr. Yuh?

DR. YUH: I think so. I don't think that there's really a disagreement in what I was saying and the rest of the Panel.

DR. PAGE: You were jumping across --

DR. YUH: Right.

DR. PAGE: -- looking at risks and benefits?

DR. YUH: Exactly.

DR. PAGE: And we will get there.

So, in terms of this narrow question, if indeed that was how it was posed to us,

Dr. Zuckerman, we will get there in terms of rolling everything up. My impression is that we're in agreement.

DR. ZUCKERMAN: Okay, fine.

DR. PAGE: Dr. Cigarroa, did you have another comment?

DR. CIGARROA: I do.

DR. PAGE: Saying none?

DR. CIGARROA: None.

DR. PAGE: You yield to Dr. Brindis?

DR. BRINDIS: To rephrase what you just said, our Chair just said, I mean, if Question 1 said "is sufficient in reducing the risk of ischemic stroke in patients with non-valvular AF," that's a very different question than "is sufficiently comparable to warfarin in reducing." A totally different question.

DR. PAGE: Okay. So with that, we'll move on to Question No. 2.

Dr. Neubrander.

DR. NEUBRANDER: The results of the PROTECT AF trial suggest that the WATCHMAN device offers an important benefit compared with warfarin therapy by lowering the risk of hemorrhagic stroke. This signal of reduced risk of hemorrhagic stroke in WATCHMAN subjects was not observed in PREVAIL.

However, the robustness of the signal is limited by:

- The observation that the hemorrhagic stroke rate in the PROTECT AF Control group was higher than expected and higher than warfarin groups in contemporary anticoagulation trials;

- Circumstances regarding PROTECT AF Control subjects who were adjudicated as having hemorrhagic stroke.

Please comment on the potential benefit and the magnitude of the benefit of the WATCHMAN device to reduce the risk of hemorrhagic stroke compared to warfarin.

DR. PAGE: Comments from the Panel. Dr. Cigarroa.

DR. CIGARROA: So as I stated just prior to the break, in a way, part of the differential in the hemorrhagic stroke is expected by descriptive pharmacologic approach in the device arm, which limits dual antiplatelet -- excuse me -- limits antiplatelet therapy coupled with warfarin therapy versus what happens in clinical practice, and so how much is device-specific versus what is attributable to warfarin coupled with antiplatelet therapy. And I think that's something the Panel needs to consider.

That said, when you sample electronic medical records and you look in the real world, patients managed medically for atrial fibrillation, even if they have not had an acute infarct or a recent stent, are often on antiplatelet therapy, and we know that increases a risk of intracranial hemorrhage threefold.

DR. PAGE: Thank you.

Other comments. Dr. Kandzari.

DR. KANDZARI: I would only support Dr. Cigarroa's comments, that I don't think the trial is disadvantaged by the fact that a number of patients in the control arm were on antiplatelet therapy simultaneously. I think that's simply representative of real-world practice and that should be expected beyond this clinical trial. The reduction in hemorrhagic stroke, I think, is very clinically meaningful aside from statistical significance.

I would only reference my other comments is that, is this really a feature related to the WATCHMAN device, or is this simply a comparison against aspirin that we see the difference? And that falls against the background that if the device permits the obviating oral anticoagulants, as is the intent, then maybe it is through, inferentially through the permission of removing warfarin resulting in that benefit. I think it's one that has to be balanced with ischemic stroke risk, as well, as we've discussed.

DR. PAGE: Dr. Furie.

DR. FURIE: I agree. I just worry that the combination of warfarin plus antiplatelet therapy in TARGET AF inflated the hemorrhage risk, and it's unfortunate if that is actually real-life management of patients with atrial fibrillation. The way the question is worded, there is potential benefit, and if in the end, you're comparing long-term monotherapy antiplatelet treatment with warfarin, it seems obvious that there would be lower hemorrhage risk in the patients treated with the antiplatelet. Whether that could actually be achieved, I guess, is the question.

DR. PAGE: Does anybody want to comment on specifically the PROTECT data in terms of the relatively high hemorrhage, for the record, as to how you synthesize that?

Dr. Brinker.

DR. BRINKER: That was one of the reasons, in the 2009 meeting, that we thought we needed more data, or that the majority of the committee did, because that hemorrhagic stroke with warfarin, that rate seemed too high to many of the people that were there at that time. So we had hoped, as Rick suggested, that the PREVAIL study would give us some support in that area, whether this was true, whether this was not true, and that this was

just a poorly controlled Coumadin function for the PROTECT group.

And one of the things that they were asked to do, I believe, was to make sure that the Coumadin was controlled, that whether, in fact, it was or not is another story because the percent in time/therapeutic range doesn't seem to be very different between the two. But what we get is what we get. And the 2013, I agree with Rick 100%, that we just -- we didn't have --

DR. PAGE: For the record, that's Dr. Lange. You said Rick.

DR. BRINKER: Oh, yeah. Dr. Lange, Rick.

DR. PAGE: Thank you.

DR. BRINKER: So that we didn't have the length of follow-up necessary to provide the data. And now, getting that follow-up, it's going in the wrong direction. Now, you say it's one or two patients over that follow-up, but the incidence of these events is so small, which is the reason why there was such a wide confidence interval in the first place, that two adverse events is meaningful.

DR. PAGE: So, just so I'm clear on what you just said, you commented on the relatively high rate in PROTECT AF. And then in PREVAIL, you made note of the fact that it was not that high, as high, in the control group; is that correct?

DR. BRINKER: Right, right. You asked what do I make --

DR. PAGE: Right.

DR. BRINKER: What does one make of the PROTECT, and I think that even from the get-go there was worry that that was -- how much higher than would be expected --

DR. PAGE: So you were worried that that was not representative, and that worry

was confirmed in your mind by the PREVAIL data? I'm not putting words in your mouth. I'm just trying to make clear what you're saying.

DR. BRINKER: Yeah. Well, I mean, as best as the numbers show, yes.

DR. PAGE: Okay, thank you.

Dr. Cigarroa.

DR. CIGARROA: And I believe that when you look at the demographics of the PROTECT versus a lot of the primary preventive trials that looked at warfarin or some of the so-called newer -- they're not newer anymore -- but oral anticoagulants, the demographic populations are different. The prevalence of hypertension is substantially higher, the presence of concomitant other comorbidities is higher, and the combination of antiplatelet therapy higher than in the other. So I'm not surprised.

DR. PAGE: So as I'm looking at the question, the question posed to us was, "Please comment on the potential benefit and the magnitude of the benefit of the WATCHMAN device to reduce the risk of hemorrhagic stroke compared to warfarin." I'm hearing that, in part, the difference may relate to the other drugs, is this aspirin versus warfarin. I'm hearing that one would expect to have a higher rate of hemorrhage perhaps given the warfarin and the fact that often in the real world there are patients taking both antiplatelet agents, as well.

I'm hearing also that the PROTECT data did seem to be an aberration, and that seemed to be perhaps confirmed by PREVAIL in terms of a very high rate of hemorrhage in the control population. What I don't hear us responding to yet, Dr. Zuckerman, is specifically the potential benefit and magnitude of the benefit. So does this provide a

benefit to patients to have the option of the left atrial occluder over not?

And I see Dr. Lange, Dr. Cigarroa, and Dr. Brinker.

DR. LANGE: Again, because of the complicated way it was described in the PROTECT AF data, I think we have difficulty. At least for the PREVAIL study, a total of four patients, two in each group, for the magnitude of the benefit, the absolute risk reduction would be 0.3%. So, if there is a benefit, if there is a signal towards that, it's not a large magnitude.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: So I would state that the potential benefit is present, the magnitude likely less than what we see presented.

DR. PAGE: Thank you.

Dr. Brinker.

DR. BRINKER: I think there's no doubt that there will be less hemorrhagic stroke if you don't have Coumadin, but I agree that the absolute magnitude compared to the incidence of ischemic stroke is going to be less. On the other hand, the effect in the person who has it is going to be much more severe.

DR. PAGE: Can you amplify on what you just said, please?

DR. BRINKER: So it's just magnitude can be measured two ways. One is the statistical incidence and the other is the devastation of the event to the person. And I think the statistical incidence is going to be high but not that greatly higher, but the effect on whoever gets it is going to be much worse.

DR. PAGE: If you're the 1 in 100 or 1 in 1,000, it's 100% for you. I think --

DR. BRINKER: Yes.

DR. PAGE: Yes, sir.

Dr. Brindis.

DR. BRINDIS: My only added comment, I do think there is benefit to the WATCHMAN device in terms of reducing the risk of hemorrhagic stroke, and the magnitude is going to be dependent on the patient population actually receiving it. We could argue, again, that shared decision making, if it's utilized in people with high HAS-BLED scores, the magnitude is going to be higher, and if it's utilized in patients who have low HAS-BLED scores, then the magnitude would be much less.

DR. PAGE: So, Dr. Zuckerman, you heard a summary of the comments that I received prior to my, kind of, pinning the Panel down further on the specific question asked. And I think what we're hearing is that there still is the question raised as to whether this is a pharmacologic effect or not related to the medicines provided, that there -- it would make sense that there would be less hemorrhage if someone isn't taking warfarin; however, the signal is not what it was in PROTECT and, furthermore, is seen to be relatively modest.

I will also mention that there are members of the Panel who are still pointing out quite accurately that in terms of the shared decision making and the devastation of a stroke when it does occur, that's a major deal. But, overall, I'm hearing that there appears to be a difference, if that would make sense, but it's not of great magnitude. Is this helpful to you?

DR. ZUCKERMAN: Yes. I would just like to know if any Panel members found the meta-analysis to be helpful for getting a better guesstimate of the potential magnitude of effect here.

DR. PAGE: And, specifically, the meta-analysis with regard to hemorrhage or when we're looking at the totality --

DR. ZUCKERMAN: No, the hemorrhagic stroke because you had one trial where people thought the rate might be too high, one trial where the rate reportedly wasn't high enough.

DR. PAGE: Thank you for bringing that up. And it might be worthwhile for the Panel to discuss their comfort with the meta-analysis. I already put Dr. Naftel on the spot, and he was warm to it. I believe he was not the person who asked for it, and this was not requested by FDA, but it is interesting. Do panelists have any comments on the meta-analysis, whether they are satisfied just taking both trials and combining them to give us guidance as to our determination today?

Dr. Furie.

DR. FURIE: I found it interesting, but it was, I thought, difficult to interpret given the methodological problems with PROTECT AF. Giving it equal weight with PREVAIL made it difficult to draw any firm conclusions.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: Yeah, I found the meta-analysis that was presented by the Sponsor that selected out the patients who had the same risk profile as PREVAIL to be easier to interpret. The meta-analysis including both total trials was a little bit difficult to interpret for the reasons Dr. Furie mentioned.

DR. PAGE: Thank you.

Any other comments about the meta-analysis? Dr. Naftel.

DR. NAFTEL: I agree with both comments, but I think it's important to understand what you're saying. In my opinion, you're rejecting the whole Bayesian approach where you're combining data from the PROTECT into the PREVAIL, so this is a huge question to me. If you don't like the meta, then you don't like the Bayesian, in my opinion.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: The concern I have is that the PROTECT AF patients are different from the PREVAIL, and so that's why I prefer the other meta-analysis, but I do think that there is a concern about lumping both studies together.

DR. PAGE: Dr. Brinker.

DR. BRINKER: Dr. Naftel, I think that this again reflects the 2013, when we brought up the point that this appeared to be, that is the PREVAIL, appeared to be a different patient population, and it's difficult to have a meta-analysis or a Bayesian analysis for that matter if your populations are different, isn't it?

DR. PAGE: Dr. Brindis.

DR. BRINDIS: I think another important point is to appreciate that the potential benefit will further increase over time the diversions related to major bleeding in the control group versus the WATCHMAN.

DR. PAGE: Thank you.

So any other comments on the meta-analysis?

(No response.)

DR. PAGE: So, Dr. Zuckerman, there is a fair amount of comfort with using this to inform our decisions, but at the same time, I'd say there's some divergence in terms of an acknowledgement that the populations don't appear to be comparable and appear to be less comparable than they were the last time they were looked at. And I've learned a lot from my statistical colleagues, and one of the things I've learned from them, I thought, was if populations aren't comparable, you really have trouble performing a meta-analysis. So Dr. Naftel is pointing out the Bayesian approach of building on the data we have available, but I'm hearing some divergence as to how much we're comfortable with the meta-analysis. Perhaps there is a little bit more comfort when you parse out the PROTECT patients and make them PREVAIL-like.

Is this adequate, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. That's very helpful.

DR. PAGE: Great, thank you. We'll move on to Question No. 3.

Dr. Neubrander.

DR. NEUBRANDER: Based on the June 2014 PREVAIL dataset in the updated Bayesian analysis that combines the PREVAIL data with 50% discounted data from PROTECT AF, the WATCHMAN device continues to not meet non-inferiority for the first primary endpoint, and no longer meets non-inferiority for the second primary endpoint. In addition, an increasing divergence between the results of PROTECT AF and PREVAIL is present.

Please comment on the clinical significance of the failure of the WATCHMAN device to meet either of the first and second primary endpoints in the PREVAIL trial.

DR. PAGE: And I open this question to the Panel. I would like you also to comment

on any issues as to the fact that this is post hoc, and that has been raised by the Sponsor. We're looking, again, at the data. But we have more data now, and so I'm interested in people's comments on the clinical significance of the results of this second analysis of PREVAIL.

Dr. Slotwiner and Dr. Kelly.

DR. SLOTWINER: I had a question, and I don't know if that's going to --

DR. PAGE: Sure.

DR. SLOTWINER: -- affect the flow, but is this post hoc? Because --

DR. PAGE: I'll look to perhaps the FDA. It's been certainly called post hoc. I believe the original, the most recent panel, the dataset was closed, and at that time, people were satisfied, so by definition -- I believe that was the case, but I'm open to Dr. Zuckerman and Dr. Naftel's perspective on that definition.

DR. ZUCKERMAN: Well, I'll start first and then Dr. Naftel can really help us. As Drs. Slotwiner and Page are pointing out, this was not the pre-specified primary analysis that we would be here again, but by the same token, these are data that we can't ignore. And so the problem becomes, regardless of what you call it, these are data that we need to deal with, and the statistical estimators or p-values that we use may become a bit more problematic, but we have to deal with it from both a clinical and statistical perspective.

Dr. Naftel.

DR. NAFTEL: The classical p-value is a more better randomized trial, and you do it once and then you go home. But within the mission of FDA to look at the product life cycle that you've educated us about, Dr. Zuckerman, the p-value really becomes a measure of

evidence of how much you believe things are similar or different, and I think it's totally appropriate to look at that p-value across time from the initial study to the later study to the later study to additional data to the post-approval study, on and on. So I mean, your mission with FDA is to decide when that p-value becomes significant, you know, when you need to pull something off the market, when you need to put it on the market. So, to me, this isn't ad hoc to me. This is science.

DR. PAGE: Thank you, Dr. Naftel.

And then so I guess, Dr. Slotwiner, to answer your question, when I commented that it's post hoc, it is by definition post hoc to the primary endpoint, but that's without judgment. As a matter of fact, from my perspective, we would be abdicating our duty in terms of safety and efficacy of the device if there's a signal that we don't examine fully. And I think we're hearing from Dr. Naftel that that's acceptable, as well.

DR. NAFTEL: That's just my opinion.

DR. PAGE: That's all we want.

(Laughter.)

DR. PAGE: I now extend the query to the Panel to comment on the clinical significance of the failure of the WATCHMAN to meet either the first or second primary endpoints in the PREVAIL trial.

Dr. Kandzari.

DR. KANDZARI: So I think everyone would be in agreement we have a trial that didn't meet now all of its two endpoints based on more completeness of follow-up and completion of PREVAIL, and the stroke rates are divergent and not paralleling each other in

the device group. And so my question, though, as we enter into this discussion of comment is that we're heavily reliant, in part, on the 50% discounting, and I know that's very standard and that was agreed upon by both FDA and the Sponsor. And, Dr. Naftel, I know this is a real over-simplification, but you know, when we do a meta-analysis, we're comparing maybe an apple, one type of apple, with another apple or an apple and an orange. Here we've got half of an apple with an orange. You know, when we're doing 50% discounting, we're really looking at the PROTECT AF data and having some influence in some domains and not in others.

And so my question for maybe Dr. Naftel and FDA on this is that were there any other analyses done, for example, in almost like a sensitivity of looking at discounting different degrees of this trial? Because if you discount PROTECT AF more, the ischemic stroke rate is going to go up; if you discount it less, it's going to amplify the benefit we see with hemorrhagic stroke.

DR. PAGE: Did you want a comment from FDA or Dr. Naftel?

DR. KANDZARI: Ideally, both.

DR. PAGE: Dr. Zuckerman.

DR. ZUCKERMAN: So a primary methodology with which Bayesian trials are planned is that there's a lot of upfront simulation work. So with simulations using this particular discounting, as well as a variety of different possibilities regarding the control and treatment event rates for the new PREVAIL trial, the Agency was reasonably convinced that this was a reasonable way to go forward. And let me define the word "reasonable" in that if there was a significant divergence of events rates between PROTECT and PREVAIL, it would

be noted in the lack of ability to meet the key three primary endpoints. And if there was further confirmation, then we would see it in the ability to meet all three endpoints as Dr. B, our statistician, has shown us at the beginning of the presentation. The actual distribution for PREVAIL looks somewhat different from PROTECT in that we're left with these results that might be characterized as difficult ones for you to decipher.

DR. NAFTEL: So I think I agree with so much of what Dr. Zuckerman says. You know, we're treating this like it's a randomized trial and all the patients are similar in one arm with the other arm, and we know that it's just absolutely not true. And that's why people like Dr. Brindis and I do risk factor analysis, to find out where the benefit is, what sort of patients benefit the most, to do predictions. In this case, if you combined all the data and performed a nice risk factor analysis, you'd probably learn more. You'd learn where the benefit is and where it isn't, although the classic statistician would be alarmed by the small number of events when you try to do the analysis.

The fact that the PROTECT patients were reduced to the ones that met the criteria for PREVAIL, you know, I took great comfort in that. But I personally think what we're down to is a better strategy for Bayesian analysis because when we look at the tables that we're looking at right now for this question, to me, it's totally do you go Bayesian or do you go with the standalone, because the results are not similar. The whole thing was built for Bayesian, and that's the way it was built and those were the rules, but maybe there should have been a node where we said not just are they poolable but a node, yes or no, do we go with Bayesian or do we go with frequentist, and then we know the whole thing wasn't built with enough power for frequentist. So I think the FDA and the scientific community needs

to re-think the application of Bayesian analysis and come up with some more pragmatic rules.

That was just me talking. I don't if I answered any question.

DR. PAGE: Thank you, Dr. Naftel. And part of that will have to taken off line with the FDA.

Dr. Lange, I'll ask you to comment on the question at hand, and that is the clinical significance of the failure of the WATCHMAN device to meet either the first or second primary endpoints in PREVAIL.

DR. LANGE: It does bother me for the reason -- I mean, the Bayesian, the size of the second study, the PREVAIL study, is based upon a 50% discount rate for the PROTECT AF trial, and the second trial is built. Does it confirm the first trial, which all of us are hoping for, or is there a signal that, in fact, the first trial, with all of its problems, doesn't show that there's a benefit? So I think the fact that it doesn't meet the non-inferiority does bother me.

DR. PAGE: Dr. Kelly.

DR. KELLY: Another thing that was a big topic at the last meeting, in 2013, was that yes, there were more ischemic strokes in the WATCHMAN group, but a lot of those were upfront strokes, and if we looked at it over time, those would sort of get diluted out and that we would see fewer ischemic strokes in the device group because people wouldn't be having the late strokes that the warfarin group is having. But we're kind of seeing the opposite of that now, and I think that's kind of concerning because that, in my mind, last time, was one of the reasons I ultimately thought well, yeah, over time it will dilute out, but

it hasn't happened. It's going the other way.

DR. PAGE: Thank you.

So, Dr. Zuckerman, with regard to Question 3, I'm hearing the Panel -- everyone wishes this were easy and that both the first and second primary endpoints were reached and instead -- so everyone's troubled by that. I think people are commenting, in part and context, to their perspective on the big picture, which we're going to get to soon. But there is concern raised by most, if not all, about the results seen and that the endpoints weren't met for non-inferiority. Does this meet your needs?

DR. ZUCKERMAN: Yes, thank you.

DR. PAGE: Thank you.

Going on to Question 4.

DR. NEUBRANDER: A potential benefit of the WATCHMAN device compared to warfarin is a reduction in long-term bleeding complications associated with the use of chronic anticoagulation therapy. Bleeding events in the WATCHMAN group in PREVAIL-only and PROTECT AF were clustered in the periprocedural period. Late bleeding rates favored the WATCHMAN group in both PROTECT AF and PREVAIL-only. However, there was no overall advantage of the WATCHMAN device versus warfarin with respect to bleeding.

Please comment on the clinical significance of the major bleeding events.

DR. PAGE: Thank you.

Dr. Kelly.

DR. KELLY: So I think this is very similar to the last question, you know, right now with the data we have, the bleeding rates overall aren't different. And so last time we

thought, well, if we give it time, the ischemic stroke rates will be different, and that didn't happen. So, at this point, I think it makes sense, but it made sense last time, too, and I don't think I'd be willing to bet at this point that they'll be different long term.

DR. PAGE: Thank you.

Dr. Kandzari.

DR. KANDZARI: I think it's fair to say, however, that we don't have good fidelity around the bleeding in these two trials, that the definitions were fairly loose and not standardized, and to make definitive comments about bleeding are challenging. That said, as I mentioned earlier in our prior discussion, half of the events were related to the procedure itself. And although we did see, in our last panel meeting, a transition in the procedural safety of this, if I look back in the data, I think the bleeding rates were only reduced by an absolute roughly 1% between PROTECT and PREVAIL.

So I would also say that -- and I know the Sponsor, as they move forward in clinical trials and in practice, that they will refine the bleeding definition as they've indicated in the postmarket surveillance study, but I think that's an opportunity in the procedural aspect to minimize bleeding if there are such ways for them to amplify that difference even more.

DR. PAGE: Can I get someone to comment on the issue that was raised, that while the bleeding overall is pointed out in Question 4, did not show an overall advantage? The perspective from the Sponsor was that if it happens while you're in the cath lab and they're in tamponade, you can take care of that. If you have short-term bleeding in the setting of the acute period, you're better off.

Does the Panel agree with that or is bleeding, bleeding and therefore we look at the

overall bleeding as opposed to essentially censoring those that happened in and around the procedure?

Dr. Cigarroa, then Dr. Lange.

DR. CIGARROA: So, if we take a look at two sets of data in different patient populations, that is bleeding associated with surgery such as coronary bypass graft surgery or bleeding associated with percutaneous coronary intervention necessitating transfusion, both of those at 3 years are associated with excess mortality. So whereas if you had asked me that question 5 years ago, I would have said, well, we can take care of it, we can transfuse it, we can support them, the data today about bleeding during procedures requiring transfusions, at least, is a major issue.

Second point I would make is that I wouldn't expect to see a difference, statistically, in bleeding rates until 6 months henceforth into this by design because patients are on aspirin and clopidogrel through 6 months before they're changed to aspirin monotherapy. And we know that the bleeding event rates on aspirin and clopidogrel are statistically similar to the bleeding rates on warfarin.

DR. PAGE: Let me just ask, but what about the periprocedural, wouldn't you expect a higher bleeding in and around the procedure?

DR. CIGARROA: Yes, but I don't think bleeding around procedures is as benign as I thought 5 years ago.

DR. PAGE: Okay, thank you.

Yes, Mr. Thuramalla.

MR. THURAMALLA: So, following up on Dr. Cigarroa's comment, if I look at the Slide

Number 72 from the Sponsor, it looks like there is less bleeding in the WATCHMAN group after the 5-month period when the patient is only on aspirin. So I would like you to comment on that, please.

DR. CIGARROA: That's what I would expect. Yeah, I expect a difference in hemorrhagic event rates in the WATCHMAN plus pharmacology arm to commence at 6 months when they're on simply aspirin therapy versus the control arm that is on warfarin and often an antiplatelet agent, as well. I would not expect a difference prior to 6 months, and in fact, there may be an excess hazard associated with the procedure.

MR. THURAMALLA: Bringing back to the context of this question, is there a clinical significance, do you think, after the 6-month period?

DR. CIGARROA: I do think there is a significant difference after. How much of that is due to our bias as clinicians in adding therapies to therapies to reduce the risk of either an infarct or stroke -- and somebody already on warfarin, there's a lot of data that you do in the absence of an acute coronary syndrome or a stent implanted within the previous 12 months to expose your patient to harm.

DR. PAGE: Dr. Brindis.

DR. BRINDIS: You know, my comments on the earlier question really dovetail actually more for this. And my nickel would be on the benefit here, as opposed to Dr. Kelly's nickel, not sure where it would be. And, again, it's the building on Joaquin's comment about the divergence again of bleeding as we're out further, just on aspirin, particularly in the WATCHMAN group, and the appreciation that many patients who have atrial fibrillation oftentimes are on dual, if not even at times triple, antiplatelet therapies in

the real world. A lot of those patients excluded, of course, from this study.

DR. PAGE: So, Dr. Zuckerman, with regard to Question No. 4 and the clinical significance of the major bleeding events, I'm hearing from the Panel that in general, bleeding is bleeding and that one needs to look at both the acute periprocedural in the early phase events, as well as ongoing where, indeed, the overall advantage wasn't seen. There is some suggestion that if especially -- if someone, if a patient with the device is on aspirin alone, one might expect reasonably that bleeding would be less frequent than patients on warfarin and certainly, as we've heard today, often on warfarin plus other antiplatelet agents. But, overall, I'm not hearing any sense that the bleeding events necessarily are swaying opinions one way or another in terms of making a decision as to this device.

Is that helpful?

DR. ZUCKERMAN: Yes, is it. Thank you.

DR. PAGE: Dr. Brinker, did I get that right?

DR. BRINKER: Maybe for everybody but me. So --

DR. PAGE: Please clarify.

DR. BRINKER: So I think bleeding is the essence here. I mean, bleeding is the major factor to consider. And it's definitely an issue of Coumadin after you get through the first 6 months, and most of these patients will have the majority of their life after the first 6 months. So this is an important consideration. If I knew for sure that the device was effective as preventing stroke as it is by withdrawing Coumadin, then I'd be very happy with the device. But here we're talking about the relative import of a bleed compared to an

increased stroke rate, ischemic stroke rate.

As Dr. Brindis says, that dovetails with the issue about bleeding, hemorrhagic stroke versus ischemic stroke. I think these are important things, and if we knew that there was a full counterbalance in both degree of illness and frequency, extent of defect and frequency between ischemic stroke and bleeding, then we would have a bigger, maybe an easier job of handling this.

DR. PAGE: Just so I'm clear, what you were helping to correct is we all agree bleeding is important, but from your perspective, you lean towards seeing this as a positive benefit by the fact that bleeding is reduced, from your perspective --

DR. BRINKER: A major positive benefit.

DR. PAGE: Okay.

DR. BRINKER: Yeah.

DR. PAGE: Thank you.

Let's move on to the proposed indications for use, Question 5.

DR. NEUBRANDER: The sponsor has proposed the following indications for use:

"The WATCHMAN LAAC Device is indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism."

Please comment on the Indications for Use statement.

DR. PAGE: Thank you.

And before I open this up to discussion, let me just comment on the issue of

indications for use, and that is that, as I understand it, our indications for use need to be informed by the data that we have in front of us. I was struck by hearing the stories of the patients, God bless them, who traveled here to express their appreciation for the device and the physicians who wanted this device, but I was hearing mostly physicians wanting this device for patients that we're not necessarily looking at today.

And we will discuss -- and my impression from the previous panel is the use of this device beyond equipoise between warfarin and the device. And to the Sponsor's credit, they've led with the fact that this is not necessarily being pushed as someone's got new A-fib, do you want warfarin or do you want a device, but nevertheless, we have to struggle with the indication as we are given guidance in terms of the regulatory system as it would be written based on the data we have at hand.

Is that a fair way of summarizing, Dr. Zuckerman?

DR. ZUCKERMAN: Dr. Page has made an extremely important statement that the Panel members really need to consider. Certainly, Drs. Neubrander and Farb have talked with this company, as well as the competitive companies, about doing the sort of important trial that Dr. Page has just mentioned. However, that is not on the table today, nor are those indications.

Thank you, Dr. Page, for pointing it out.

DR. PAGE: So Dr. Cigarroa and then Dr. Patton.

DR. CIGARROA: So it's interesting. It says it's indicated to prevent thromboembolism from the left atrial appendage and would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism. So I agree that the risk of

stroke and systemic embolism compared to no therapy would be true, but in this case I think it would be more appropriate to comment that the composite event rate of stroke is what we're talking about because the signal on the thromboembolism or on ischemic stroke, I don't know where the ischemic strokes are coming from. Are they peri-device or are they gaps, are they due to comorbidities?

And so I would be much more comfortable with a statement to reduce the combination. It's a composite endpoint. I don't know how we could state that it's this. I do agree that the overall component, when you include ischemic and hemorrhagic stroke, as patients receive treatment with an intention-to-treat analysis, is reasonable.

DR. PAGE: Thank you.

Dr. Patton.

DR. PATTON: I think --

DR. PAGE: Your microphone is on, Dr. Cigarroa.

DR. PATTON: I think I might even consider going a step further in that what this indication is missing is the fact that the device plus pharmaceuticals is not non-inferior. And I wonder if working that into this definition of the indication would be helpful with this tightrope we're trying to walk between what we know from the studies that we have and knowing that there are patients who are not indicated for anticoagulation therapy. But there is also a very large group of patients out there who are underserved, who technically would be recommended for warfarin therapy but for many reasons may, as a patient preference choice, do not wish to avail themselves of that therapy, who need an alternative.

DR. PAGE: And just so I'm clear, you would want to be able to offer this to that patient who says I don't want warfarin but I want something?

DR. PATTON: Yeah. And I think that it's possible that one of the ways we can think about doing that is by altering the indications to make it clear that this is suboptimal compared to oral anticoagulation, even with respect to the reduction of risk and stroke and systemic embolism.

DR. PAGE: And I'll need guidance from FDA as to how we say that. You were describing an indication that states that it's not --

DR. PATTON: Second-line therapy.

DR. PAGE: It's failed -- exactly. And, again, just to bring us to the issue at hand, we don't have that option. We have to come up with an indication that is true to the data, and every patient that was shown to us today was eligible for warfarin.

DR. PATTON: I think that's -- I think I'm not making my point very clearly, is that I think there might be a way to word the indication as such to make it clear that this therapy is not non-inferior to oral anticoagulation but still could be a possibility in the way that, for example, Dr. Yuh describes bioprosthetic valves compared with mechanical valves with respect to longevity.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: So I want to agree very much with you. So the wording, I think there's a logic problem. If you go to your cardiologist, you're in A-fib and he or she says I recommend warfarin therapy, then we're done. There's no more discussion. You go with

the recommendation, I'm done. So this doesn't really make sense to me. Maybe it should say patients who are eligible for warfarin therapy or candidates or something, but if they've been recommended, there's no more discussion unless the doctor says hey, I've got two alternatives that are roughly equivalent, which do you want. But if he or she has recommended, then we're done.

DR. PAGE: I think it was interesting hearing from the Sponsor that patients need to be able to tolerate warfarin, but this would be patients who can tolerate the warfarin but not necessarily are recommended warfarin.

Okay, thank you.

DR. ZUCKERMAN: Dr. Page, it may be useful for Dr. Farb to give a little bit more of an introduction to why the possible indication stands as it is right now in framing this discussion.

DR. PAGE: Thank you, Dr. Zuckerman.

DR. FARB: I'll be very brief. The reason that we didn't choose to discuss the word "eligible" is because now we have other anticoagulant agents out there, the NOACs, so those patients would be eligible for warfarin, all these other agents, and we only have data for warfarin, so the idea that these patients are recommended, for whatever reason, to be on warfarin -- and that may be for various factors, cost, availability, formulary, whatever, but the decision has been made or recommended by the physician to recommend that particular anticoagulant.

DR. PAGE: It seems like there's such a moving target there. I wonder whether you considered that putting in the indication the actual $CHADS_2$ or CHA_2DS_2-VASc score, which

by definition makes them eligible for warfarin, but also the other NOACs.

DR. FARB: Well, once again, since we didn't have any information on NOACs, we wanted to sort of keep that out of the indications for use. And also data sometimes change, and we've seen sort of a transition from the $CHADS_1$ patients getting aspirin to now CHA_2DS_2-VASc, and so it may be a moving target. We wanted -- again, I think this reflects the previous panel -- to give the flexibility to the physicians to work with the data and the patients to come up with the best treatment proposal.

DR. PAGE: And if I can point out, all the data are from -- the Sponsor's not suggesting anything but warfarin be provided as the anticoagulant at the time of implant; is that correct? I'm seeing a nod, thank you.

Dr. Brinker.

DR. BRINKER: So I remember from our last meeting that there was an impassioned plea that this wasn't for anybody who would be recommended to have warfarin but rather for high-risk patients; for bleeding; this, that, or the other thing. And I think this is a change, actually, to the best of my recollection, from what we were left with in 2013. This basically says anyone needs to be -- is thought to be best treated, who needs warfarin, can have this instead as an alternative. And I'm not sure that with the level of information we have now, that that should be -- the doctor shouldn't say, well, you can have either this or that, whatever you want.

DR. PAGE: Well, if I may comment. Based on guidelines, and a number of us who have been involved in guideline writing, this says "may be considered," kind of like a two-way recommendation --

DR. BRINKER: I know, but it doesn't --

DR. PAGE: -- as opposed -- is indicated.

DR. BRINKER: But do we want to say that?

DR. PAGE: Great question.

DR. BRINKER: That's the issue.

(Laughter.)

DR. PAGE: So what do you want?

DR. BRINKER: I would like -- if we were talking about approving this today, I would like something that sort of characterized the patient as being either at high risk for bleeding with standard warfarin or cannot take it for other reasons.

DR. PAGE: Thank you. I see Ms. Chauhan and Dr. Kandzari.

I do think that in a subsequent question we're going to be kind of wrapping this all up because, as I prefaced when we started this out, we are limited as to what the indication can say. But, also, we need to have the discussion because what I'm hearing from the Panel is the previous indication likewise didn't -- people weren't intending for this to be equivalent therapy to warfarin even at that panel.

Ms. Chauhan.

MS. CHAUHAN: I would just like to ask you to clarify your response to Dr. Patton because I've been thinking along the same lines that I thought I heard her. What about second line, that warfarin is choice, but as Dr. Yuh pointed out, sometimes you need another alternative for patients who won't or can't accept that choice.

DR. PAGE: You bring up a very good point, and that's what we're wrestling with. We

could say it's indicated for patients for whom warfarin is second line if those were the patients that were studied. For this, for all the data we've seen today, they were warfarin candidates. So these are not second-line patients; these are first-line patients. So that's what we're struggling with. How could we configure an indications for use that we could then vote on that is based on the data we've been presented and is true to those data when actually I'm hearing from the Panel the sentiment that -- and from the Sponsor -- this is not do you want warfarin or the device; this is for a special subset of patients. But we're wrestling with the regulatory process, if I'm getting that correctly, Dr. Zuckerman?

DR. ZUCKERMAN: Yes.

DR. PAGE: Thank you.

(Laughter.)

DR. PAGE: Dr. Kandzari.

DR. KANDZARI: So I'm going to step back even further away from the warfarin issue. I think we're in alignment about the second-line statements, but it's hard to do that when both endpoints are not met. Let me be the devil's advocate, and I'll ask my Panel colleagues for you all to convince me of this: The device is indicated to prevent thromboembolism from the left atrial appendage. Now, based on intuition, that makes complete sense to me. But if thromboembolism and ischemic stroke are surrogates, how do we know it's preventing thromboembolism? And what I've heard today is the Sponsor say it's not preventing ischemic stroke; it's higher. I've heard that, well, we know it's better, though, because of an imputed placebo analysis from an entirely separate population not treated, I think, with anything. So I'd like to hear some comments about the statement preventing

thromboembolism.

DR. PAGE: Dr. Cigarroa and then Dr. Lange.

DR. CIGARROA: So, David, I agree with you. As I opened up earlier today, to me it's combined stroke event driven primarily by a reduction in hemorrhagic event, and so the ischemic strokes are higher. Where they're from, I don't know. And, on balance, it's a reduction in hemorrhagic stroke. So I agree with you.

DR. PAGE: Dr. Lange.

DR. LANGE: I'm just a simple guy, but if something's not non-inferior, it's inferior. And I agree with my colleague, Dr. Kandzari, who's -- I'm not sure that we actually have proven that it's decreased thromboembolism of the left atrial appendage. And the only way to make this informative is it may be considered for patients with yada-yay-yada who would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism and want inferior therapy.

DR. ZUCKERMAN: Okay. So Dr. Lange --

(Laughter.)

DR. ZUCKERMAN: -- that's going a little bit afield. The indications for use statement is just one part of the label. Its primary purpose is to indicate the patient population and what the device can do. As you know, we have a clinical trials section that can fully elaborate on results from trials. We can put in other wording when we believe that it's important to emphasize other things when considering use of a device. And, certainly, the comments have been very helpful, but I think if we can get back to Dr. Farb's comments, it may help us wrap this up.

DR. FARB: Thank you, Dr. Zuckerman.

So I think when we read the sentence as a sentence without stopping -- so "to prevent thromboembolism from the left atrial appendage," that's all this device is intended to do, period. And with respect to "would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism," it really gets to why the patients are on warfarin therapy; it's to reduce the risk of stroke and systemic embolism. And so read in continuity, that's why the patients are recommended to be on warfarin, and those are the patients for whom we have data for this particular device.

DR. LANGE: But, again, I would suggest the data shows it's inferior, and if I said the same thing, that we were going to give them black tea for this indication but it wasn't shown to be effective, we wouldn't be having this conversation. I mean, the only people -- "considered for patients who would be recommended for warfarin and want inferior therapy."

DR. PAGE: In all fairness, Dr. Lange --

DR. LANGE: Right

DR. PAGE: -- we'll discuss this when we wrap things up, but I know you're being facetious; no indication would say that. And there is a sentiment that I think the previous panel, the majority, and at this panel have that this may have some role in some patients. And I don't think you would disagree with that having heard the patient comments, but your point is well made.

Dr. Furie.

DR. FURIE: I was just going to argue that maybe parsing out -- the ability to tolerate

warfarin for a short period of time is different than having to be on it chronically. And given that it's required at least for the first 45 days, somehow that the indication for use may reflect that necessity.

DR. PAGE: May I just ask, of -- what was it -- the 5% that end up on warfarin chronically, are they then committed to warfarin and you don't think they can take it for more than 45 days?

DR. FURIE: Well, it's the same problem as having --

DR. PAGE: It's a tough one.

DR. FURIE: -- an acute coronary syndrome and having a stent put in the next day and then having to deal with triple antithrombotic therapy.

DR. PAGE: Fair enough.

Dr. Slotwiner.

DR. SLOTWINER: I just want to answer the question directly, which is I don't feel comfortable with this indication for use. I think we're in a regulatory bind, but to answer Dr. Zuckerman's question specifically without coming up with qualifying statements, which I would feel are reasonable, but to answer this particular question about this indication, I think the evidence just doesn't support it.

DR. PAGE: I'm going to take a stab at wrapping this up, Dr. Zuckerman, because we will not be able to wordsmith this indication today.

DR. KANDZARI: Dr. Page.

DR. PAGE: Yeah.

DR. KANDZARI: Can -- right here.

DR. PAGE: Oh, Dr. Kandzari.

DR. KANDZARI: Can I just wordsmith one part, though? Is that I think --

DR. PAGE: Go for it.

DR. KANDZARI: -- the best we could say for the thromboembolism component is that the device would be indicated to reduce stroke or all-cause stroke comparable to warfarin therapy, because the meta-analysis suggested equipoise with regard to the balance of hemorrhagic and ischemic.

DR. PAGE: Okay, I'm not sure everybody on the Panel would agree with that.

But let me just suggest, Dr. Zuckerman, that this is going to be a tough one. It seems to me the first sentence would be more appropriate to look at what the indication is in terms of the true endpoint that was studied, if you at least believe the endpoint or at least believe you came close to achieving the endpoint, and that would be the combined endpoint of at least all stroke or the endpoint used as a primary endpoint for the PREVAIL trial.

The device is designed to occlude the left atrial appendage for sure, and the issue of what to do with the warfarin and with other novel oral anticoagulants is a struggle; to say that they are warfarin eligible, they clearly have to able to take warfarin for at least a period of time if they're going to be considered for this device, and there's no option for a novel oral anticoagulant in this. So I'm afraid we're not adequate in meeting the needs of the question, but if we're going to get this done today, I don't believe we'll be able to wordsmith this indication.

DR. ZUCKERMAN: The high-level comments have been excellent. We're ready to go

on to the next question.

DR. PAGE: Great, thank you.

Dr. Neubrander.

DR. NEUBRANDER: The sponsor has presented comprehensive data from two randomized controlled trials (PROTECT AF and PREVAIL) and two continued access registries (CAP and CAP2).

Based on the totality of the data, do the probable benefits of the WATCHMAN device outweigh the probable risks?

In answering this question, please comment on the topics on the next slide.

And I'll just read Part (a) for now: Do the results of PREVAIL and PROTECT AF support the central role of thromboembolism from the LAA in the pathogenesis of ischemic stroke in patients with non-valvular atrial fibrillation? Please comment on the relative effectiveness of a local (WATCHMAN) vs. systemic (warfarin) therapy.

DR. PAGE: Why don't you go ahead and read (b) also, please?

DR. NEUBRANDER: Sure. Okay, Part (b): Do the safety and effectiveness results from PROTECT AF and PREVAIL indicate that the WATCHMAN device is a clinically acceptable alternative to warfarin therapy?

DR. PAGE: Thank you.

This is where we really come down to it. I'm interested in comments from the Panel as to when you wrap things together, do the probable benefits outweigh the probable risks in this population?

(No response.)

DR. PAGE: Somebody jump in. I promise others will join you.

Dr. Cigarroa, thank you.

DR. CIGARROA: So I'll take a stab at it.

Number 1 is that, from a patient perspective, what is not measured is quality of life. And I think that is something that we need to consider. With regards to Part (a), the relative effectiveness of local versus systemic warfarin therapy for reducing ischemic stroke is not supported by the data; the Sponsor stated that and we've had extensive discussions. When one combines that with safety, in the real world -- and I think that mirrors what is seen in the combination of antiplatelet with warfarin therapy, I do expect that the hemorrhagic intracranial hemorrhage rates will be lower, and the morbidity and mortality associated with those are devastating.

DR. PAGE: Thank you. Other comments.

(No response.)

DR. PAGE: This is what we're going to be voting on pretty soon, so I really want an active discussion. I'd like to hear from as many of us as possible so I can get an idea to summarize.

Ms. Chauhan.

MS. CHAUHAN: Looking at it from the patient perspective, I'm just mindful that there is a significant cohort of patients who are eligible for warfarin who choose not to use it. And it seems to me that a decision tree for the physicians, in their training, would be a way to look at this, too, that if they're warfarin eligible, long-term warfarin eligible and they refuse it, then you move down the decision tree to consider this. That would make sense to

me because I think we cannot ignore that a significant number of people who are eligible refuse warfarin and it becomes not only a quality of life but a quantity of life issue.

DR. PAGE: Dr. Slotwiner.

DR. SLOTWINER: So, in answer to Question (a), local therapy being effective, I think as the Sponsor and as Dr. Cigarroa said, clearly it's not equivalent. But I think, looking at the data comparing non-treated patients, there's clearly a benefit to occluding the left atrial appendage. But there are other sources of embolic stroke, and I think that's been an important lesson for me.

In answer to Question (b), is the WATCHMAN clinically an acceptable alternative to warfarin therapy, I think that that's going to have to be answered with qualifying statements. It can't be considered equivalent.

DR. PAGE: Dr. Brindis.

DR. BRINDIS: I'm just going to build on some of the earlier comments and maybe start it off with what's going on in the real world. We appreciate that 50% are being treated. And we have an alternative therapy that people are utilizing, the so-called LARIAT device, which has a 510(k) approval, hasn't had the rigor that the Sponsors have now had with three panels, two clinical trials, multiple registries. And the device is now, to my understanding, been used in over 2,000 patients.

I can't compare apples with oranges, but it may have a procedural complication rate that is substantially higher. It is a procedure that is certainly technically more complicated to do in terms of requiring a septal puncture and a dry pericardial tap, and as I think about what's happening, what will happen to our patients as they look for alternative therapies,

we may be in a situation where patients will be increasingly utilizing a device which may be an increasing hazard that's studied less with less clinical data.

That's not to say this is a reason that we should go forward, but it tells me that (1) the FDA didn't even ask us about issues related to safety of this device because we've answered that question. We felt, based on the last panel, particularly with the due diligence of the Sponsor in terms of new sites, whatever, we felt it was safe. The challenge now is the efficacy, and I think we all have huge questions about the efficacy. But maybe it is safe and effective without -- in a way that we appreciate patients who might not choose to have Coumadin therapy. So I'm very much wrestling with these issues and just wanted to explore those with others.

DR. PAGE: Thank you.

And let me -- Dr. Noonan.

DR. NOONAN: I want to amplify some of the things Dr. Brindis just said. I'm in interventional neuroradiology and went through this back in the early '90s with Guglielmi detachable coils to treat brain aneurysms when the alternative was a surgical alternative, namely opening your head, pushing the brain apart, finding the vessel, and putting a clip on it. We didn't have a medical treatment for brain aneurysm and we still don't. And here we compare -- it's not a perfect device; there is no perfect device. There will be iterations of this device as it's approved that will probably be better than this first generation device.

But in any case, we're comparing a surgical device. It's an endovascular surgical device with a really darn good medical therapy as long as the patients follow the medical therapy. But there are a lot of patients who can't follow the medical therapy, and the list of

contraindications for taking Coumadin is tremendously long. You could read the list; it's in the package insert. And a lot of patients will have to go off Coumadin, so what do we have to offer for them?

DR. PAGE: Great, well said.

Let me -- Ms. McCall.

MS. McCALL: I'll make it fast. When patients are first diagnosed with A-fib, they're overwhelmed with information. But the upside of that is we get a lot of options. We've got lots of choices for rate control and rhythm control, and now with the NOACs we have lots of options beyond warfarin for anticoagulation. I really think the WATCHMAN is a new option that can be offered after the patient and their physician have had an informed discussion and come to a decision together on what's best for the patient.

DR. PAGE: Thank you for bringing that perspective.

Let me toss something out to the Panel. I'm hearing from the Panel contrary sentiments, and I think this is what we're wrestling with. Our indications are "have to be informed by the trials" and the trials show, unfortunately, that this did not meet the endpoint. We hear the Sponsor saying that they're not advocating this to be brand new patient who is warfarin or NOAC eligible, but we're also hearing from the Sponsor, ourselves and certainly patients, that there ought to be something else out there. So, hypothetically, we're kind of bound, but I frankly think that the last vote represented a panel in favor of this device being available as a second line.

So, hypothetically, if you'll work with me for a second, if it were going to be a second line, how would you make sure that it is a second line? For example, if the indication has to

be informed by the trial, then one way or another it's going to say may be indicated or whatever, but it's going to be around what the patients who were studied included. So how might you protect the patient and make sure the options are available? For example, would you have a more clear intention for use, would you have a questionnaire, some sort of external process to make sure that people are doing this right? There was an allusion to what's going on in Europe. That can't inform what we're doing, but it was at least reassuring that in general these aren't being put in as first line but being put in as second.

So, hypothetically, Dr. Zuckerman, if you'll permit this, can we take two or three minutes to describe how might you set this up so it's not just a free-for-all putting these in if they were voted for approval today?

Dr. Slotwiner.

DR. SLOTWINER: I think we all have a sense of which patients we feel would probably -- we would want to consider for this study or this device if it were approved, understanding the limitations today. And we can wordsmith that now or later, but I think the real question is what would happen when it got out for use generally? And I think that some prospective registry that monitored and kept track of data and is incorporated in the postmarket approval trial would be one tool that I think could be very effective to do this.

DR. PAGE: Thank you.

Dr. Noonan.

DR. NOONAN: With regard to other endosurgical devices, one of the ways it's been done in the neuro realm is to require proctorship by a physician as mandatory. In fact, with some devices you have to have five proctored cases followed by five additional cases. Here

the device maker has only requested that proctorship be optional. I don't think it should be optional. That's one way to ensure that it's going to be used properly.

DR. PAGE: Thank you.

Any other comments? Am I accurately reflecting the sentiment of the Panel?

Yes, Dr. Naftel. And Dr. Furie.

DR. NAFTEL: So I've been having trouble mentally framing how all this is working, and I just want to say the way you described it is exactly the way I was thinking, so I appreciate it.

DR. PAGE: I'm not sure what that means, Dr. Naftel.

(Laughter.)

DR. PAGE: Is that good or bad?

DR. NAFTEL: It's a wonderful thing.

DR. PAGE: Thank you very much.

Dr. Furie and then Dr. Brindis.

DR. FURIE: I thought the issue you were getting at was whether it would be used in the real world with good judgment when the patient was giving informed consent as opposed to the technical ability of the interventionalist or the cardiologist. But --

DR. PAGE: And is that what you're favoring?

DR. FURIE: Yeah. I think that it's an issue that, how this is framed, as whether it's a first-line alternative to anticoagulation versus a second-line less-effective option which may be better than nothing and how you would actually operationalize that.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: Well, I would just agree with that comment. If you have a really good patient consent form that really describes the options well, appreciates the risk, have them understand the concept, and maybe this is a case to think a little bit about the team approach in the same way we, with TAVR, have set up that a couple physicians are involved in the decision making, a surgeon and a cardiologist; maybe in this case having a neurologist and a cardiologist to work together with the patient with that decision-making tool to go forward on the second-line therapy at this time.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: So I would concur. I think that in the prior panel in December 2013, we applauded the Sponsor for their educational program for bringing on the new sites in PREVAIL, and we looked at that data, and the results were outstanding. I think, really, here the issue is understanding what the trade-offs are and making sure, in the shared decision making, that patients understand excess ischemic. We haven't shown that it's non-inferior, but it is an alternative in this patient population coupled with the very important fact that it's been studied with ongoing antiplatelet therapy. We don't know yet. There are some small data samples that have been reported out, single site or from Europe, on shortened duration of antiplatelet therapy or not utilizing warfarin therapy post-discharge.

DR. PAGE: Thank you very much.

So, Dr. Zuckerman, I know you're capturing -- and by recording -- this robust discussion as the Panel is weighing the questions, specifically Question No. 6, which is the

bottom line here as to whether the totality of the data suggest that the benefits outweigh the risk. I also am hearing people wrestle with the fact that we are being asked one question in terms of indication based on the patients studied, and there is sentiment that while perhaps this does not meet the necessary rigor for that indication, there is the sentiment that we wish this were available for certain patients. How can we best answer this question for you or will it come down to -- or going on with the actual voting questions and our explanation for our votes?

DR. ZUCKERMAN: Well, first, I want to thank the Panel members for this in-depth discussion. Certainly, like the FDA team, we're struggling with the overall benefit-risk here. I think all of us, perhaps, may agree with Dr. Slotwiner -- please speak up -- that in certain patients, the benefit-risk may be acceptable. But where the discussion has been most helpful is, I think there is a feeling that if this device were to be approved, it's incumbent on the Sponsor and FDA to try to maximize the intent with which appropriate patients get this device. It's not an alternative for every warfarin-eligible patient, and the Sponsor has recognized that.

Now, what can the FDA do in that respect? Number one, there's been a good discussion about how patients are actually informed. And I would ask you to look at the patient guide, which is the next section, as well as the label. And I don't personally think the patient guide informs a patient appropriately at all, and in very difficult cases like this, we can require that an independent physician and patient have a discussion and that be signed off.

Secondly, the Sponsor can agree to a controlled rollout, again, to enhance the

certainty that appropriate patients do get a certain device therapy, and I think that's within the possibilities here. But the bottom line is that shortly, the Panel will be asked to vote on the current data even with the uncertainties, and you'll need to make a decision. But certainly, in the post-approval period, if there is a sentiment for moving forward, I think the Agency has heard quite clearly that this is a special type of device that needs special rigor as we continue to monitor its use regardless of decisions.

DR. PAGE: I think you've heard from us clearly that this is a special device and that it is not -- and I'm looking around to make sure I'm getting it right. The perspective of the Panel is unanimous that this is not something that a warfarin-eligible patient -- it's one versus the other. This is for a select population. I'm looking at the Panel, and I'm seeing nods.

So Dr. Noonan had a comment or question, and then I want to move on to Question 7 because the hour is getting late.

DR. NOONAN: This will be quick. Dr. Zuckerman can probably answer it. In neuro, we have a class of device called HUD devices, Humanitarian Use Device. They're exempt devices for certain patients and not all patients certainly. Would you have any comments regarding that type of category?

DR. ZUCKERMAN: Okay, this would not qualify for that particular program, but what it would qualify, again, for is continued appropriate oversight if it is eventually approved. But that's a question mark right now.

DR. PAGE: Great, thank you.

Dr. Neubrander.

DR. NEUBRANDER: Please discuss whether the proposed labeling is acceptable or whether modifications are recommended.

DR. PAGE: I'm looking to the Panel for any comments on the labeling, and Dr. Zuckerman mentioned the patient information. This is a tough one for me, based on the discussion that I'm hearing. I'm looking for someone in the Panel to provide some commentary for the FDA on this; otherwise, Dr. Zuckerman, I'm not sure we have a lot to inform the FDA other than concerns that this really be a major issue to work out between the FDA and the Sponsor. But comments from the Panel?

Dr. Cigarroa and then Dr. Slotwiner.

DR. CIGARROA: I would just say I think that the robust discussion we had in the prior question lets the FDA and Sponsor know our concerns about the labeling as it stands.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: I again don't want to go into details in labeling, but I think I have concern about how patients will be educated to make an informed decision. I certainly entirely think that it has to be a shared decision, but I'm concerned that it's very difficult to give them objective information in certain situations. So the booklet as it stands, I think, has room to go.

DR. PAGE: So I might even go so far as to say that there's a lot of work to be done on the labeling, and certainly the patient information, if that were to occur. And it would need to reflect not necessarily the regulatory requirements related to this if this were approved based on the patient study but rather what you're hearing strongly from the Panel, and that

is, this is a special device, that if it's going to be approved at all, should be placed in special patients who are not otherwise your typical, easily managed patients for warfarin or a NOAC actually. Am I capturing the sentiment of the Panel adequately?

Does that do the job for you, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it does. Thank you.

DR. PAGE: Thank you very much. Let's go on to Question No. 8.

Dr. Neubrander.

DR. NEUBRANDER: Yes. In response to recommendations from the December 2013 panel, the sponsor increased the sample size of the proposed post-approval study to enroll 1,000 new WATCHMAN subjects, which will be combined with up to 579 subjects currently enrolled in CAP2. For this combined WATCHMAN subject cohort, the PREVAIL primary endpoints will be tested against performance goals.

Given the new information from the WATCHMAN studies, please comment on the adequacy of the post-approval study and provide additional recommendations, if needed.

DR. PAGE: Comments about the post-approval study.

Dr. Brindis, thank you.

DR. BRINDIS: With the conflict that I'm the senior medical officer of the National Cardiovascular Data Registry -- you know, if the study had shown efficacy, then my enthusiasm for what was offered by the Sponsor would be reasonably good, although I would have some other suggestions in terms of looking at what's going on in the community in the PINNACLE Registry, for example, in terms of patients on oral anticoagulation or on patients not. But with the substantial questions that have been raised by the studies and

discussions by the Panel, I'm wondering that if the FDA decides to move forward under a change in label as a second-line therapy, which I am feeling is the feeling of the Panel, that all patients who have the device implanted be followed in a national registry, and that would probably be well accomplished through the NCDR, either through the CathPCI Registry or the ICD Registry, without being an infomercial.

DR. PAGE: Thank you for that perspective. You have great insight into the area of registries obviously, and the conflict that you put forward at the beginning of your statement. Thank you.

Dr. Brinker and then Dr. Kelly.

DR. BRINKER: It sort of bothers me, Dr. Brindis, that you say if efficacy had been established. Then we have to doubt whether we can approve something if it's not efficacious. I voted for this device twice already for approval, and each time I felt, gee, there needs to be something. And each time more information was garnered. There doesn't seem to be any help in that way. What we would really like is something definitive to tell us that we're doing really good here rather than a status quo, if you will.

So I would -- and we can't use -- Bram, that we can't use a post-approval study to determine efficacy. We might be able to use it to gather more information, but we can't use it to determine. So we should think carefully about what's done if we're not sure that it's efficacious.

DR. ZUCKERMAN: So those were great comments, Dr. Brinker, but it's a reasonable assurance of effectiveness that you'll be voting on shortly, and I'm sure you're aware of that. And, certainly, in the post-approval period, we can try to increase the precision

around our assumed effectiveness. But you're right, there needs to be something there before a device is approved.

DR. PAGE: I would just remind us, though, this is assuming that if it were approved, the post-approval study. Anybody have comments? Do people like this? Is this better than the one before? Is this enough?

Dr. Naftel and then Dr. Kandzari.

DR. NAFTEL: So I like both the idea of a registry or the plan, as stated. The thing I want to say is FDA, in the last few years, has been so sensitive and so good with these postmarket studies, it's been a real emphasis, and they've happened. I'd say in this case, it really needs to happen and it needs to happen on a timetable. We don't need to be here a year from now saying, oh, we've got a study plan, so I would strongly encourage a timetable. And I'm reacting just a little bit to the fact that some of the data was supposed to have been given to us before the panel meeting last year, but it was inadvertently left out, and that's part of the reason we're here, so just reacting a little bit to that in a friendly manner. I'm saying there needs to be a specific time, you know -- May 2015 -- there needs to be times to look at it because however we vote, if we do approve, it's all going to be with some uncertainty and with some trepidation, so we need this post-approval study.

DR. PAGE: Dr. Kandzari, did you have a comment?

DR. KANDZARI: Yes, I did.

It sounds like the Sponsor is willing to commit proctorship for all of these new sites that become available in a postmarket surveillance registry, and I would only emphasize that again, because we have more and more information that, at least in the setting of

complex PCI proctoring, improves outcomes and success. And I think the continued access program in this realm was a good example of that.

What I was really going to make the point for, however, is the post-approval study, if approved, is that with approval of new technologies and drugs, oftentimes an indirect benefit is the education around the disease space itself and the disease condition. And atrial fibrillation we've heard a lot about today, but we can always learn more. And I think one of the areas that we learn more -- and we've talked about real-world practice -- is the combination of antithrombotic and antiplatelet therapies. And so I think there needs to be dedicated surveillance of patients' adherence and prescription of antiplatelet and antithrombin therapies in this type of study.

DR. PAGE: Great, thank you.

Dr. Brinker.

DR. BRINKER: So I think the weak link in this study is not needing more devices, but needing an enriched control group, especially to see what PREVAIL was reflective of: just a very chancy fortunate group of control patients or whether that's really the state of the art. So I would suggest that the Sponsor and the FDA consider not a randomized controlled trial anymore but a prospective registry of people who are getting newly anticoagulation therapy. And they might also include NOAC to have some information about the comparison of events in that group to the events in the WATCHMAN group. So that's all I have to say about it.

DR. PAGE: Thank you.

Dr. Lange and then Dr. Kelly. I do want to remind us the hour is getting late, and I

want to get to the voting questions while we're all as sharp as we are right now.

Dr. Lange, Dr. Kelly.

DR. LANGE: I won't be any sharper 10 minutes from now than I am now or less sharp.

(Laughter.)

DR. LANGE: Two issues. One is I totally agree with Jeff. In the CAP2, 579 patients, we have a 2.7% ischemic stroke rate in the first 6 months, and the allegation is that, well, first of all, it's going to -- the hazard ratio looks like it's going to get worse later on. We have no control group and the control group now is thought to be a low -- artifactually low. So I agree with Jeff. If we're going to offer this to individuals and say you have an option, some will take Coumadin and those that don't get this device, we'll have a control group if they're otherwise matched similarly.

DR. PAGE: Dr. Kelly and then Dr. Naftel.

DR. KELLY: Just addressing the number of 1,000 patients. I think it's hard at this point to know if 1,000 is plenty or not because we don't have a homogenous population, so if they all were PREVAIL patients and all met all those criteria, but right now we've got PROTECT people and we've got PREVAIL people with different risk factors, and so it could be 1,000 of a complete mishmash, and I don't think we'll be anywhere further than we are now.

DR. PAGE: Dr. Naftel.

DR. NAFTEL: So with total respect to my colleagues, I fear if we had a control group -- so it wouldn't be a randomized trial, it would be a mishmash, and we've already had the

randomized trial with all these issues. If we had a new control group, how did they get in there? We'd be really talking about apples and oranges. And what you want is a good idea, but I think it's just asking too much of a post-approval study.

DR. PAGE: Brief clarifying comments from Dr. Cigarroa and Dr. Slotwiner.

DR. CIGARROA: The control would further be compounded by the difficulty that -- I think just last month the data coming out is 62% of new prescriptions prescribed for primary prevention of thromboembolic events in AF are the newer anticoagulants.

DR. PAGE: Thank you, good point.

Dr. Slotwiner.

DR. SLOTWINER: I do think that this would be a great opportunity to combine the postmarket approval study with a registry. I won't belabor the point, but I support that concept.

DR. PAGE: Dr. Zuckerman, if I may summarize, the post-approval domain is as important here as any other discussion that I've participated in. There's real concern about how this will be implemented and what we can learn from a post-approval study. There's been a comment about possibly having a control. I understand that that would be very problematic. The issue of a registry was raised, and likewise, that might further inform the issue. I might suggest that, again, this will take some real work to look at this carefully because this is very, very important for this device. I would also take the opportunity, with any sort of ongoing post-approval study, to really nail down how the device is being used and in what patients, so I think that's critically important. I've heard that from the Panel.

Dr. Cigarroa.

DR. CIGARROA: And, again, the ongoing registry. And I would like Dr. Brindis to comment --

DR. PAGE: I'm actually not going to have him comment.

DR. CIGARROA: Okay.

DR. PAGE: We've got to move on.

DR. CIGARROA: All right. Sorry.

DR. PAGE: Dr. Zuckerman.

DR. ZUCKERMAN: I think the FDA and Sponsor got a good idea where we should be moving. Thank you.

DR. PAGE: Good, thank you.

It's now time for the Panel to hear summations, comments, or clarifications from the FDA, and then the final word would go to the Sponsor. Both the FDA and the Sponsor are allowed 10 minutes. You'll get no more than 10 minutes. If you take less than 10 minutes, we'd be okay with that. But feel free to take the time you need as long as it's not more than 10 minutes.

Welcome back, Dr. Neubrander.

DR. NEUBRANDER: Thank you. And I won't take 10 minutes.

So, first of all, FDA would like to thank the Panel for their time and attention and informative discussion here today regarding the WATCHMAN PMA. As you've heard earlier today, we're here because of the new events in the PREVAIL trial that raised questions about the benefit-risk profile of the WATCHMAN device. This is definitely a challenging dataset to analyze, and we appreciate the Panel's insights.

PREVAIL was, in many ways, a better executed trial, and compared to where we were at the December panel meeting, we have over 800 patient-years, which is substantially more follow-up from PREVAIL-only. What this means is that although the PREVAIL-only data were not powered to stand alone, the study now carries much more weight in considering the totality of the WATCHMAN device safety and effectiveness information. Based on updated PREVAIL information, there was concern whether the WATCHMAN device provides adequate protection from ischemic stroke and systemic embolism in atrial fibrillation patients. There are important limitations to the analysis of the hemorrhagic stroke signal that call into question the robustness of the rate difference between the WATCHMAN device and warfarin observed in PROTECT AF. In addition, there are options available in the form of the NOACs that have a reduced risk of hemorrhagic stroke compared to warfarin. The vast majority of cardiovascular or unexplained deaths were not linked to the WATCHMAN device or to warfarin, and there was a signal of reduced late bleeding with the WATCHMAN device, as expected, but no difference in overall bleeding rates.

Thank you very much for the opportunity to share our comments with the Panel on a device that may be useful for patients who have reason to not be on long-term warfarin.

DR. PAGE: Thank you very much. Now we'll ask the Sponsor to come forward.

Dr. Stein.

DR. STEIN: Likewise, I'd like to thank each of the Panel members for the robust and considered analysis today. FDA has asked this Panel to reevaluate the benefit-risk of WATCHMAN based on the new data since the December 2013 panel. This morning, Dr. Farb

said that ischemic strokes are what is most relevant to the device. But I ask you to consider what's most relevant to patients, and that is the overall combined primary endpoint in all of our trials: all stroke, all systemic embolism, and cardiovascular death. Since the previous panel, there have been 10 new endpoint events in the WATCHMAN arm of PREVAIL and 5 new endpoint events in the warfarin arm. This exactly matches the 2 to 1 randomization and is exactly what you would expect if the two therapies are comparable. Furthermore, even for ischemic stroke only, we have shown you that the WATCHMAN device has performed consistently across all of the trials, PROTECT, CAP, PREVAIL, and CAP2, after accounting for underlying patient risk profiles.

The question that's been raised about divergence in PREVAIL is not related to device performance then. It is directly related to the fact that there was only one ischemic stroke in the warfarin arm of PREVAIL. And as you heard from Dr. Reddy, this has not been replicated in any other contemporary clinical trial, and we cannot reasonably believe that it would be replicated in real-world clinical practice.

Today, we've shown you that the full totality of the data should leave no doubt that WATCHMAN provides comparable results to warfarin for the combined primary endpoint of stroke, systemic embolism, and cardiovascular death and that it is superior for the clinically important endpoints of hemorrhagic stroke, of disabling stroke, and perhaps most importantly of cardiovascular death.

We agree fully that this device is not and should not be seen as a broad, first-line replacement for oral anticoagulants. Patients who are doing well on oral anticoagulants, patients who are anticipated to continue to do well on oral anticoagulants ought not to be

considered for this device. But there is a group of patients in the U.S. who do need access to this innovative, proven, life-saving, and as you heard, life-enhancing therapy. Who are those patients?

They are exactly the patients who entered into our clinical trials. Patients who were eligible to take warfarin but who had such good reasons to prefer an alternative that they were willing to enroll in an experimental therapy of an experimental trial of an entirely novel, new, invasive device. I ask you to remember these patients, and I ask you to consider their needs as you deliberate and as you vote on this issue.

Thank you.

DR. PAGE: Thank you very much. Before we proceed with the vote, I'd like to ask Mr. Thuramalla, our Industry Representative; Ms. Chauhan, our Consumer Representative; and Ms. McCall, our Patient Representative, if they have any additional comments.

Mr. Thuramalla.

MR. THURAMALLA: I would like to take this opportunity to thank both the Sponsor and the FDA for a very thorough presentation, and to the speakers during the Open Public Hearing. It was very helpful and gave us a different perspective from both the patients and their treating physicians. While the next session goes on to the voting, I would like to repeat the same thing as the Sponsor, Dr. Stein, mentioned, that -- and also we all agreed -- this device could potentially be beneficial to at least a select few AF patients. With that, I thank you.

DR. PAGE: Thank you very much.

Ms. Chauhan, do you have any other comments?

MS. CHAUHAN: I still believe that it is appropriate for a subset of patients and hope the Panel will consider that.

DR. PAGE: Thank you very much.

Ms. McCall, do you have any comments?

MS. MCCALL: Well, we've discussed apples and oranges, and I think this is a choice that every patient that is appropriate should -- they should have this discussion with their physician. And I think this is an option that should be in an atrial fibrillation patient's toolkit.

DR. PAGE: Thank you very much.

I want to thank the three of you. You really enhance our process. You've been active members in our deliberation, and we very much appreciate that. I will remind everyone that our Industry, our Consumer, and our Patient Representatives do not vote nor do I unless there's a tie.

We're now ready to vote on the Panel's recommendation to FDA for this PMA. The Panel is expected to respond to three questions related to safety, effectiveness, and risk versus benefit. Ms. Waterhouse will now read three definitions to assist in the premarket approval application voting process.

Ms. Waterhouse.

MS. WATERHOUSE: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket approval applications that are filed with the Agency.

The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefit to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid scientific evidence as defined in 21 C.F.R. 860.7 is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. The valid scientific evidence used to determine the effectiveness of a device

shall consist principally of well-controlled investigations as defined in paragraph (f) of the section unless the Commissioner authorizes reliance upon other valid scientific evidence which the Commissioner has determined is sufficient evidence from which to determine the effectiveness of a device even in the absence of well-controlled investigations.

The Sponsor has proposed the following indications for use:

"The WATCHMAN LAAC Device is indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism."

We will now proceed to the vote. The following questions relate to the approvability of the WATCHMAN LAAC Device. Please answer them based on your expertise, the information you reviewed in preparation for this meeting, and the information presented at the panel meeting.

Panel members, please use the buttons on your microphone to place your vote for the following three questions.

Voting Question 1 reads as follows: Is there reasonable assurance that the WATCHMAN LAAC Device is safe for use in patients who meet the criteria specified in the proposed indication? Please vote now.

(Panel vote.)

MS. WATERHOUSE: Voting Question 2 --

DR. BRINDIS: Chair?

DR. PAGE: Yes, sir.

DR. BRINDIS: So I just want to make it clear that we're voting for the proposed indication without any alteration in the indication, just to be absolutely clear.

DR. PAGE: I think that is a fair summary. You've heard that there is some opportunity to readdress the indication, but right now we have no choice but to vote on this indication. So yes, you got that right.

DR. BRINDIS: Thank you.

MS. WATERHOUSE: Voting Question 2: Is there reasonable assurance that the WATCHMAN LAAC Device is effective for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

MS. WATERHOUSE: Voting Question 3: Do the benefits of the WATCHMAN LAAC Device outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

MS. WATERHOUSE: So on Question 1, the Panel voted 12 yes that the data shows reasonable assurance that the WATCHMAN LAAC Device is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 6 yes and 6 no, the Chair voted as a tiebreaker and voted no, that there is reasonable assurance that the WATCHMAN LAAC Device is effective for use in patients who meet the criteria specified in the proposed indication.

On Question 3, the Panel voted 6 yes, 5 no, and 1 abstain that the benefits of the WATCHMAN LAAC Device outweigh the risks for use in patients who meet the criteria

specified in the proposed indication.

DR. PAGE: Thank you, Ms. Waterhouse.

I will now ask the Panel members to discuss their votes. I would like to go around the table and have each Panel member state how they voted on each question so it can be entered into public record. Please also discuss the reasoning for your vote. If you answered no to any question, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer.

I'll start on this side with Dr. Patton.

DR. PATTON: I voted yes on safety. I voted yes on efficacy because I thought that although the device was not non-inferior to warfarin, it seemed like it had a clear clinical benefit. And I voted no on Question 3 because I felt like the indication, as written, was quite broad with respect to the findings of non-inferiority.

DR. PAGE: So again, you voted yes, yes --

DR. PATTON: Yes, no.

DR. PAGE: No. Because of the indication. Thank you.

DR. ZUCKERMAN: Okay. Dr. Patton, I know the time is late, but Dr. Page's point was if you could just help us, how would you change the indication?

DR. PATTON: This hearkens back to the discussion that we had for quite some time with respect to there being patients who should be able to avail themselves in this therapy, but it has to be made clear that this device, that it is not responsible to offer this device as first-line therapy equivalent to warfarin.

DR. ZUCKERMAN: Thank you.

DR. PAGE: Thank you.

Dr. Kandzari.

DR. KANDZARI: I voted for the safety question, No. 1, yes; for the efficacy question, no; and for the balance of risk-benefit, yes. And I think, like all of us, we were very challenged and this represented, by our total vote in this issue, of the indication that Dr. Brindis raised and the discussions that we had around the indication language.

My concern regarding the efficacy is the trajectory of higher ischemic stroke, the acknowledgement among everyone here that ischemic stroke was not necessarily reduced with this technology, who it is -- intuitively, whose primary purpose is to do so. But on the other hand, for the risk-benefit balance, I'm swayed by the composite or the balance of reducing hemorrhagic stroke, however it may be compared with warfarin and/or combined antithrombotic therapy. And like others, I struggle with the indication, but I am also swayed by people moving to Vancouver to get this therapy as well. And I think that somehow we need -- my vote of yes is more of a message that somehow we need this technology in clinical practice, although I also do not fully endorse the indication as it is written.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: I voted yes for safety, yes for effectiveness, and yes for the benefits. I had a really difficult time with this, more than usual, and even though you stated that we're voting on the indications as they are, I actually voted on what I think the indications are going to be as a result of the discussion. So maybe that wasn't totally kosher, but it is what I did. So I'm a little uneasy, and I look forward to the post-approval study, and I think we'll

keep looking at slices in time at this. If not the Panel, certainly FDA will.

DR. PAGE: Thank you, Dr. Naftel.

Dr. Brindis.

DR. BRINDIS: Yes on 1, on safety. No on 2. And I was wrestling between voting yes or abstaining on 3, but I would have given the exact answer that Dr. Kandzari did for 3, and the reason why I abstained is, one, I'll be looking forward to the label revision and hopefully could change that to a yes.

DR. PAGE: So, just so that I'm clear, you abstained --

DR. BRINDIS: I abstained.

DR. PAGE: -- on the third question? Thank you.

Dr. Furie.

DR. FURIE: I voted yes on safety; no on efficacy, largely because of the proposed indication and agree with the comments that have already been made about changing that to make it clear that it's not for all warfarin-eligible patients. And then, in light of the failure to demonstrate non-inferiority, I voted no on Question 3.

DR. PAGE: Thank you very much.

Dr. Lange.

DR. LANGE: I voted yes-no-no. And Dr. Furie actually summarized my thoughts exactly. My afterthought would be with regard to patients that don't qualify for Coumadin, my encouragement to the FDA is have a randomized trial because those patients, how we administer the anticoagulation in the setting of putting this device in, whether they receive none, full Coumadin, not for people that have high risk of bleeding, it's going to

substantially impact how it's used. So my caveat.

DR. PAGE: Thank you very much.

Dr. Yuh.

DR. YUH: Yes. I voted yes on all three. I mean, I was really impressed with the Sponsor's interpretation and presentation of the data, including the extra events. I think they took a conservative approach whenever they could, and I think that, as a second-line alternative to Coumadin, which I really ultimately think this will be used for, used as, that I think it is an effective therapy. And I think, as a consequence of that, the benefits do outweigh the risks, so that's the rationale behind the three yes votes.

DR. PAGE: Thank you.

Dr. Noonan.

DR. NOONAN: I voted yes on all three, and I want to concur with Dr. Yuh and Dr. Naftel, particularly Dr. Naftel with regard to 3. I know that the indication, as actually written in the package insert, is going to change, and that's my hope.

DR. PAGE: Thank you.

Dr. Kelly.

DR. KELLY: So I voted yes for safety and no for the other two based mainly on the indication as well as the fact that the PREVAIL study was not positive. And I'm having some trouble using the meta-analysis because I don't think the populations are that similar.

DR. PAGE: Thank you.

DR. ZUCKERMAN: Okay. Quickly, Dr. Kelly, what about the comments regarding if the indication is changed as a second-line therapy?

DR. KELLY: You know, I hate to be concrete, but I don't think I'm comfortable using the totality of the data anymore. I think they're diverging, I think the populations are different, and I'm just not convinced.

DR. PAGE: Thank you.

Dr. Brinker.

DR. BRINKER: I have difficulty with the data as well. However, I voted yes for all three, and I made my own, à la Naftel, judgment about the indications. And for Voting Question 2, I circled "reasonable assurance" and then I put in "for use in appropriate patients." And for Voting Question 3, I also put in "benefits were satisfied for use in appropriate patients."

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: I voted yes on all three. I think that safety is not an issue for me, although there is an issue of early thrombus formation that at least clinically did not appear to confer an excess risk of thromboembolic events. I utilized, for Question 2, latitude with the term "reasonable." I think that the data troubles me, and I vacillated and ultimately used a lot of latitude with "reasonable." And the third, risk-benefit ratio driven primarily by the reduction in hemorrhagic stroke, which I think is devastating when it does occur more so than the reduction in ischemic stroke.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: I voted yes-no-no because I felt I had to take the questions literally,

but I fully agree with the sentiments expressed that I hope the Sponsor and the Agency will work together to revise those, and I wasn't sure who was going to vote yes and no, so I felt I had to.

DR. ZUCKERMAN: Okay. So, Dr. Slotwiner, can you be a little bit more concrete? Is the no changeable depending on the final label, or is it similar to Dr. Kelly's comment that the data just aren't there?

DR. SLOTWINER: I'm glad you asked. The no is definitely changeable. I think it really depends on the final label. I don't feel comfortable with the broad indication as labeled, and so I didn't think that the safety/effectiveness ratio could be commented on. But I do agree that with rewording and clearly stating that this is a second-line --

DR. PAGE: Can I keep just one conversation here, Dr. Brinker? Sorry.

DR. SLOTWINER: And clearly indicating in the indications that this is not equivalent to warfarin but for a second-line therapy, I would feel comfortable with that.

DR. PAGE: Thank you, Dr. Slotwiner.

Dr. Cigarroa has a comment.

DR. CIGARROA: I failed to mention that my vote on the third, on indication, is exactly assuming that that would happen based on the Panel's strong discussion, and so I assumed and trust that that will happen and voted yes accordingly.

DR. ZUCKERMAN: Thank you.

DR. PAGE: And now it's my opportunity to give my comment. I always hope I won't need to vote. I did not need to vote on the first one, but I would have voted yes. On the second one, I saw what I didn't want to see, and that was 6 to 6, and I had to vote no

because I was being literal in terms of the indication.

Thank you, Dr. Brindis, for taking me off the hook for my final vote, but I would have voted in favor, and I'll explain why. I think this device is important technology. We've heard it, I've seen it, we've got to have it available, but it's got to be available for the right people. The indication as written, it's unfortunate. We are, for regulatory reasons, bound by the patients who were studied, but I heard consensus from everyone in the room, including the Sponsor, that this is not first-line. I did hear Dr. Stein, you said you made it clear that you wouldn't take someone off warfarin, but I'm assuming you also wouldn't start them on this device if they were warfarin eligible, and I would strongly state that that's the case.

So it's a bit inconsistent to give a yes-no-yes, but I would have because I also think the message would have been appropriate. I think this device has a home, and we just need the FDA and the Sponsor to work together to develop a description for indication that's appropriate and gives this important technology a place in our armamentarium to care for our patients with atrial fibrillation at risk of CVA from embolic stroke. So that was my thinking as I went through my voting process.

I do want to thank the Sponsor, first of all, for doing an excellent job and making things very clear, being very responsive; likewise, the FDA. And I want to especially extend my appreciation to our Consumer and our Patient Rep and our Industry Rep and to this Panel. I think this Panel got it right. And the next work is for this device to not be first-line therapy but to potentially be available to patients for whom it's needed.

Dr. Zuckerman, is there anything that you would like to say before we close?

DR. ZUCKERMAN: No, I agree with you. I want to thank you and the Panel members for an excellent day's work.

DR. PAGE: Thank you. With that, the October 8th meeting of the Circulatory System Devices Panel is now adjourned. Safe travels.

(Whereupon, at 5:55 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

October 8, 2014

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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ED SCHWEITZER

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